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⑮ SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY.

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GB-A- 2 079 755
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US-A- 4 263 289

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 8. Edit. Pergamon Press, New York (1990), Chapter 60, p. 1446

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Description

The invention relates to novel soft steroids having anti-inflammatory activity, pharmaceutical compositions containing said soft steroids and novel chemical intermediates useful in the preparation of the steroids.

5 Successful predictions on a rational basis of the biological activity of compounds leading to new drugs are the main objective of drug designers. This has usually been achieved by considering a known bioactive molecule as the basis for structural modifications, either by the group or biofunctional moieties approach or by altering the overall physical-chemical properties of the molecule. Thus, the main aim has been to design, synthesize, and test new compounds structurally analogous to the basic bioactive molecule which have, 10 however, improved therapeutic and/or pharmacokinetic properties. Although "vulnerable" moieties have been identified as the ones whose role is the bioinactivation or metabolic elimination of the drug after it has performed its role, little or no attention has been paid in the drug-design process to the rational design of the metabolic disposition of the drugs. This has been the case despite the fact that the toxicity of a number of bioactive molecules is due to their increased elimination half-life, stability, or other factors introduced 15 during the design of increasing their activity. Drugs and particularly their metabolic processes contribute to the various toxic processes by formation of active metabolites. The phenomenon of metabolic activation to macromolecules is the initial step in cell damage. It is also clear that the most toxic metabolites will not survive long enough to be excreted and identified; thus, studies of the stable metabolites may provide misleading information.

20 It is clear that, in order to prevent and/or reduce toxicity problems related to drugs, the metabolic disposition of the drugs should be considered at an early stage of the drug-design process. This is true particularly when one considers that the body can attack and alter chemically quite stable structures and that, even if a drug is 95% excreted unchanged, the unaccounted small portion can, and most likely will, cause toxicity.

25 "Soft drugs" can be defined as biologically active chemical compounds (drugs) which might structurally resemble known active drugs (soft analogues) or could be entirely new types of structures, but which are all characterized by a predictable in vivo destruction (metabolism) to nontoxic moieties, after they achieve their therapeutic role. The metabolic disposition of the soft drugs takes place with a controllable rate in a predictable manner.

30 The present inventor has found five major classes of soft drugs. One of the most useful classes was termed the "inactive metabolite" approach which can be advantageously employed to design especially valuable "soft drugs." This approach starts with a known inactive metabolite of a drug or a drug class; followed by modifying the metabolite to resemble structurally (isoteric and/or isoelectronic) the active drug (i.e., activation); and designing the metabolism of the activated species to lead to the starting inactive 35 metabolite after achieving the desired therapeutic role, without the formation of toxic intermediates (i.e., predictable metabolism). The "inactive metabolite" approach further allows controlling the rate of metabolism and pharmacokinetic properties by molecular manipulation in the activation stage. Also, if no useful inactive metabolite is known, one can be designed by the introduction of transporting groups in noncritical structural parts.

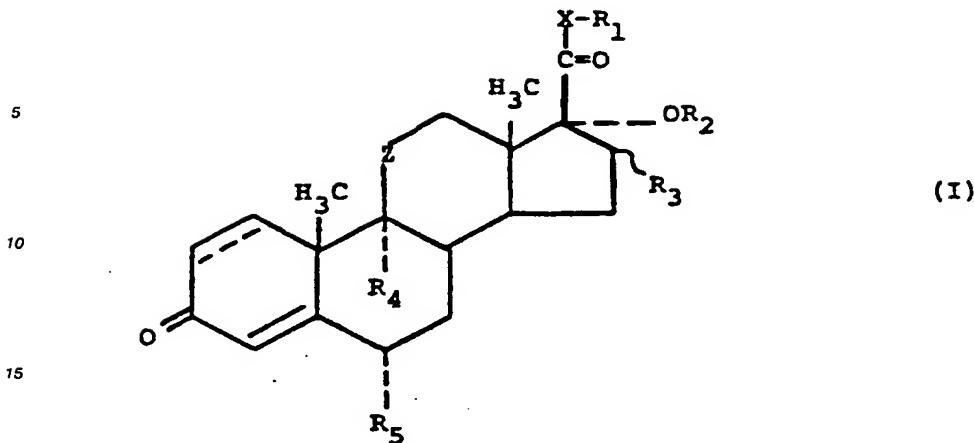
40 GB-A-2079755 relates to anti-inflammatory steroids which have 17 α -carbonate function.

US-A-4,263,289 relates to anti-inflammatory steroids which have a 17 α -acyloxy (or-hydroxy) function.

US-A-4,093,721 relates to anti-inflammatory steroids which have a 17 α -acyloxy function.

The present inventor has now applied his inactive metabolite approach to the case of the natural and synthetic glucocorticosteroids and has designed the soft steroid anti-inflammatory agents of the present 45 invention, beginning with the known or analogously designed inactive natural metabolites of the glucocorticosteroids. Thus, for example, in the case of hydrocortisone, one of its major, inactive metabolites, cortienic acid, i.e., 11 β , 17 α -dihydroxyandrost-5-en-3-one-17 β -carboxylic acid, has been used as a starting point and activated by the introduction of suitable nontoxic 17 α - and 17 β -substituents, which activated derivatives will cleave in vivo, at the 17 β -position, and possibly also the 17 α -position, after accomplishment 50 of their nontoxic role, to predetermined or designed inactive metabolites, e.g., non-toxic moieties.

In accord with the foregoing, the present invention provides novel soft steroids having anti-inflammatory activity, said steroids having the structural formula



20 wherein R₁ is C₁-C₁₀ alkyl; C₂-C₁₀ (monohydroxy or polyhydroxy)alkyl; C₁-C₁₀ (monohalo or polyhalo)alkyl; or -CH₂COOR₆ wherein R₆ is unsubstituted or substituted C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl or C₂-C₁₀ alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,

25 $-\text{NHC}(=\text{O})-(\text{C}_1-\text{C}_{10}\text{ alkyl})$

and

30

$-\text{OC}(=\text{O})-(\text{C}_1-\text{C}_{10}\text{ alkyl})$,

35 or R₆ is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxy carbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)-carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R₁ is -CH₂CONR₇R₈ wherein R₇ and R₈, which can be the same or different, are each hydrogen, lower alkyl, C₃-C₈ cycloalkyl, phenyl or benzyl, or R₇ and R₈ are combined such that -NR₇R₈ represents the residue of a saturated monocyclic secondary amine; or R₁ is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to R₆; or R₁ is

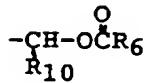
45 $-\text{CH}-\text{Y}-\text{(lower alkyl)}$
R₉

wherein Y is -S-, -SO-, -SO₂- or -O- and R₉ is hydrogen, lower alkyl or phenyl, or R₉ and the lower alkyl group adjacent to Y are combined so that R₁ is a cyclic system of the type

50

$-\text{CH}-\text{Y}$
alkylene

55 wherein Y is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms; or R₁ is

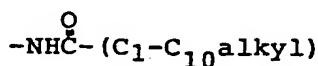


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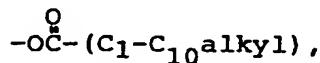
wherein R_6 is defined as hereinabove and R_{10} is hydrogen, lower alkyl, phenyl or haloalkyl;

R_2 is unsubstituted or substituted $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_3\text{-C}_8$ cycloalkenyl or $\text{C}_2\text{-C}_{10}$ alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,

10



15 and



20

or R_2 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxy carbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl;

25 R_3 is hydrogen, α -hydroxy, β -hydroxy, α -methyl, β -methyl, $=\text{CH}_2$, or α - or β - OR_2 wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen, fluoro or chloro;

R_5 is hydrogen, fluoro, chloro or methyl;

X is $-\text{O}-$ or $-\text{S}-$;

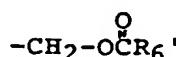
30 Z is carbonyl or β -hydroxymethylene;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated.

A group of preferred compounds of formula (I) consists of those wherein:

35 R_1 is $\text{C}_1\text{-C}_6$ alkyl; $\text{C}_1\text{-C}_6$ (monohalo or polyhalo)alkyl; $-\text{CH}_2\text{COOR}_6$ wherein R_6 is $\text{C}_1\text{-C}_6$ alkyl; $-\text{CH}_2\text{-Y-}$ ($\text{C}_1\text{-C}_6$ alkyl) wherein Y is $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{O}-$; or

35



40 wherein R_6' is $\text{C}_1\text{-C}_6$ alkyl or phenyl;

R_2 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, phenyl, benzyl or $\text{C}_1\text{-C}_6$ (monohalo or polyhalo)alkyl;

45 R_3 is hydrogen, α -hydroxy, α -methyl, β -methyl or α - OR_2 wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen or fluoro;

45 R_5 is hydrogen or fluoro;

Z is β -hydroxymethylene;

and X and the dotted line in ring A are defined as hereinabove.

The invention further provides anti-inflammatory quaternary ammonium salts of selected compounds of formula (I), as discussed in further detail below. Novel intermediates to the compounds of formula (I), e.g., 50 the corresponding compounds wherein R_1 is hydrogen, are provided also.

The soft steroids of formula (I) and the quaternary ammonium salts thereof are extremely potent local antiinflammatory agents; however, by virtue of the fact that their facile *in vivo* destruction leads only to the inactive steroid metabolite, the present compounds have far less systemic activity than the known glucocorticosteroids from whose inactive metabolites they are derived. Indeed, many of the compounds of the present invention are entirely devoid of systemic activity. Such minimal -- or non-existent -- systemic activity means that the compounds of the present invention can be used in the local (e.g., topical) treatment of inflammatory conditions without the serious systemic side effects which attend the use of the known glucocorticosteroids.

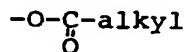
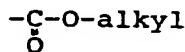
With respect to the various groups encompassed by the generic terms used here and throughout this specification, the following definitions and explanations are applicable:

5 The alkyl, alkenyl and alkylene groupings can be straight or branched-chain groups containing the aforementioned number of carbon atoms. Likewise, the alkyl portions of the alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy carbonyl, alkanoyloxy, haloalkyl, monoalkylamino, dialkylamino, monoalkylcarbamoyl and dialkylcarbamoyl groupings each can be straight or branched-chain. The term "lower" used in conjunction with any of those groupings or in conjunction with "alkyl" is intended to indicate that each alkyl portion therein can contain 1 to 8 carbon atoms.

10 Specific examples of alkyl radicals encompassed by formula (I), whether as specific values for R_1 or R_2 , or as a portion of a R_1 , R_2 , or R_3 group, include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl and their branched-chain isomers, as well as their straight and branched-chain higher homologues in the instances where "alkyl" can contain more than 8 carbon atoms. The alkenyl radicals can be exemplified by vinyl, propenyl and butenyl. Illustrative of the cycloalkyl and cycloalkenyl radicals are cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl. The alkylene moieties are typified by trimethylene, 15 tetramethylene and the like.

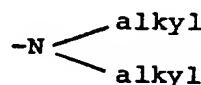
The alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy carbonyl, alkanoyloxy, monoalkylamino, dialkylamino, monoalkylcarbamoyl and dialkylcarbamoyl groupings are of the type

20
 -O-alkyl
 -S-alkyl
 -SO-alkyl
 -SO₂-alkyl

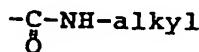


-NH-alkyl

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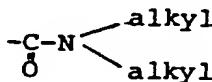


40



45

and



respectively, wherein alkyl is as hereinbefore defined and exemplified.

50 With respect to the structural variables encompassed by the group of preferred compounds of formula (I) identified hereinabove, the term " C_1-C_6 alkyl" is used to refer to a straight or branched-chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl and the like. In addition, the term " C_1-C_6 (monohalo or polyhalo)alkyl" is used to refer to a straight or branched-chain alkyl group having 1 to 6 carbon atoms substituted with from 1 to 3 halogen atoms, the term "halogen" as used herein including a chlorine atom, a bromine atom, an iodine atom or a fluorine atom. Specific examples of the contemplated monohaloalkyl and polyhaloalkyl groups include chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1-chloroethyl, 2-chloroethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 1,2-dich-

loroethyl, 1-chloropropyl, 3-chloropropyl, 1-chlorobutyl, 1-chloropentyl, 1-chlorohexyl, 4-chlorobutyl and the like. Also, the term "C₃-C₈ cycloalkyl" is used to refer to a cycloalkyl radical having 3 to 20 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

When R₁ in formula (I) is -CH₂CONR₇R₈ wherein -NR₇R₈ represents the residue of a saturated monocyclic secondary amine, such monocycles preferably have 5 to 7 ring atoms optionally containing another hetero atom (-O-, -S- or -N-) in addition to the indicated nitrogen atom, and optionally bear one or more substituents such as phenyl, benzyl and methyl. Illustrative of residues of saturated monocyclic secondary amines which are encompassed by the -NR₇R₈ term are morpholino, 1-pyrrolidinyl, 4-benzyl-1-piperazinyl, perhydro-1,2,4-oxathiazin-4-yl, 1- or 4-piperazinyl, 4-methyl-1-piperazinyl, piperidino, hexamethyleneimino, 4-phenylpiperidino, 2-methyl-1-pyrazolidinyl, 1- or 2-pyrazolidinyl, 3-methyl-1-imidazolidinyl, 1- or 3-imidazolidinyl, 4-benzylpiperidino and 4-phenyl-1-piperazinyl.

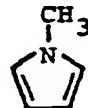
Selected compounds of formula (I), i.e., compounds wherein R₁ is α -haloalkyl, readily form the corresponding soft quaternary ammonium salts which are likewise useful as soft anti-inflammatory agents. Thus, for example, the selected haloalkyl derivative of formula (I) can simply be reacted with a tertiary 15 amine ($\geq N$) or an unsaturated amine ($\geq N$) to afford the corresponding quaternary ammonium salt. The reactants are generally used in approximately equimolecular proportions and the reaction is conducted in the presence of an inert solvent (e.g., ether, acetonitrile, CH₂C₁₂, CH₃NO₂, dimethylformamide, or the like), at a temperature of from room temperature to the reflux temperature of the solvent, for approximately 2 to 24 hours. Alternatively, the reaction can be conducted in the absence of a solvent by mixing the two 20 reactants together and maintaining them at room temperature or between 20° to 70°C for 2 to 24 hours. In either case, the crystalline salt formed can be purified by crystallization from an ether-ethanol mixture, or the like.

The expression "unsaturated amine" used above denotes N-heterocyclic unsaturated systems having 3 to 10 members in the ring, and substituted derivatives thereof, where the unsaturation corresponds to the 25 maximum number of non-cumulative double bonds, provided that the nitrogen atom contains no hydrogen atom as a substituent. The following examples will sufficiently illustrate the scope of the defined term:

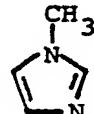
30 1-Methylazirine



35 1-Methylpyrrole



40 1-Methylimidazole



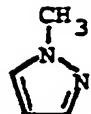
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1-Methylpyrazole

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Pyridine

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Pyrazine

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Pyrimidine

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Pyridazine

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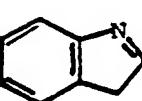
2-Methylisoindole

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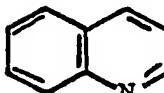
3H-indole

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Quinoline

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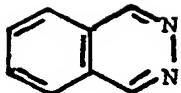
Isoquinoline

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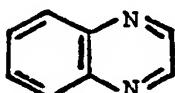
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Phthalazine



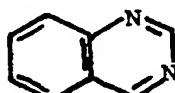
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Quinoxaline



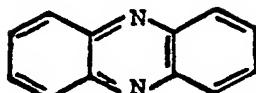
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Quinazoline



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Phenazine



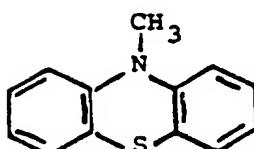
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Isothiazole



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10-Methylphenothiazine



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Isoxazole



35

Furazan



40

Substituted derivatives of the unsaturated amines include groups as shown above containing one or more alkyl, -COO(alkyl) or -OCO(alkyl) substituents.

With respect to the expression "tertiary amine," this expression denotes amines wherein the nitrogen atom has no hydrogen atoms attached thereto and which are not among the N-heterocyclic unsaturated systems encompassed by the expression "unsaturated amine" as defined above. Typically, the term "tertiary amine" includes trialkylamines, wherein the alkyl groups, which can be the same or different, each preferably contain 1 to 8 carbon atoms; trialkoxyamines wherein the alkoxy portions each contain 1 to 8 carbon atoms; tertiary saturated cyclic amines such as quinuclidine or substituted quinuclidine (e.g., 3-acetoxyquinuclidine); and N-substituted derivatives of secondary saturated cyclic amines [e.g., an N-substituted derivative of morpholine, pyrrolidine, imidazolidine, pyrazolidine, piperidine or piperazine,

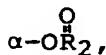
wherein the N-substituent can be a group such as $(C_1-C_8)alkyl$, optionally containing additional substituents such as methyl.

Preferred quaternary ammonium salts include those derived from 1,2-dimethylpyrrolidine, 3-acetox-
5 yquinuclidine, 1-methylpyrrolidine, triethylamine and N-methylimidazole. Especially preferred are the quater-
nary ammonium salts derived from the reaction of the aforesaid amines with compounds of formula (I)
wherein Z is β -hydroxymethylene and R₁ is chloromethyl, most especially when R₂ is lower alkyl.

While all of the compounds encompassed by formula (I) above essentially satisfy the objectives of the present invention, nevertheless certain groups of compounds remain preferred. A "first" group of preferred compounds of formula (I) has been set forth in the Summary of the Invention hereinabove.

10 Another preferred group of compounds consists of the compounds of formula (I) wherein Z, X, R₁ and R₂ are defined as hereinabove, and the remainder of the structural variations are identical to those of hydrocortisone (i.e., R₃, R₄ and R₅ are each a hydrogen atom and the 1,2-linkage is saturated) or of prednisolone (i.e., R₃, R₄ and R₅ are each a hydrogen atom and the 1,2-linkage is unsaturated), most especially when R₁ and R₂ are as defined with respect to the "first" group of preferred compounds set forth
15 hereinabove.

Another preferred group of compounds consists of the 6 α - and/or 9 α -fluoro and 16 α -or 16 β -methyl congeners of the compounds indicated in the preceding paragraph. Within this group, the compounds
20 wherein Z, X, R₁ and R₂ are defined as hereinabove and the remaining structural variables are identical to those of fludrocortisone, betamethasone and dexamethasone are particularly preferred, most especially when R₁ and R₂ are as defined with respect to the "first" group of preferred compounds set forth
hereinabove. Other compounds of particular interest within this group are those wherein Z, X, R₁ and R₂ are defined as hereinabove and the remaining structural variables are identical to those of triamcinolone, flumethasone, fluprednisolone or paramethasone, particularly when R₁ and R₂ are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Yet other interesting compounds are those
25 wherein Z, X, R₁ and R₂ are defined as hereinabove, R₃ is



30

and the remaining structural variables are identical to those of triamcinolone, particularly when R₁ and R₂ are as defined with respect to the "first" group of preferred compounds set forth hereinabove.

In each of the groups of compounds indicated in the three preceding paragraphs, the compounds
35 wherein X is oxygen are particularly preferred. Most especially preferred are the compounds encompassed by the groups indicated above wherein Z is β -hydroxymethylene, wherein X is oxygen, wherein R₂ is C₁-C₆ alkyl (particularly methyl, ethyl, propyl or isopropyl), and wherein R₁ is C₁-C₆ alkyl, C₁-C₆ (monohalo)alkyl (particularly chloromethyl) or -CH₂-Y-(C₁-C₆ alkyl) wherein Y is defined as hereinabove (particularly when the C₁-C₆ alkyl group is methyl).

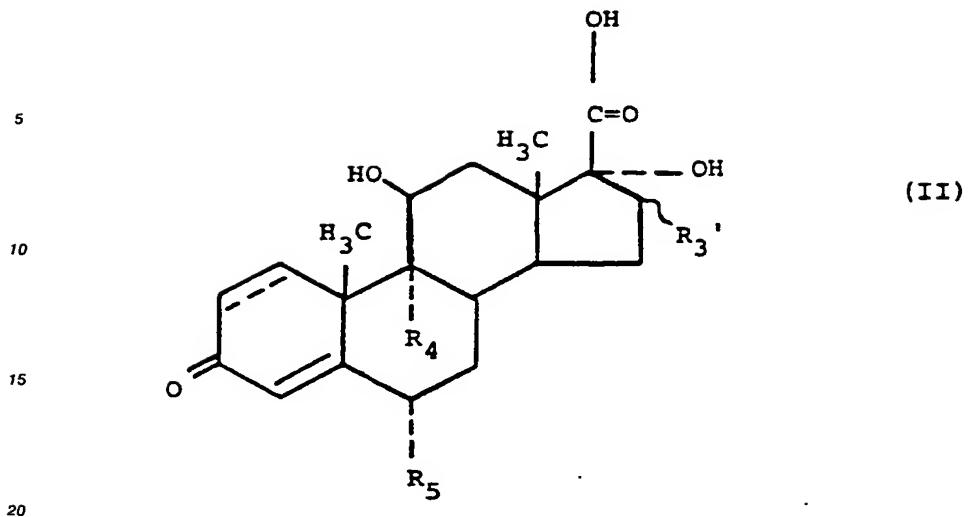
The compounds of formula (I) can generally be prepared by known methods, the method of choice
40 being dependent on the identity of the various substituents in the desired final product.

One generally useful method for the preparation of the compounds of formula (I) wherein Z is β -hydroxymethylene and X is oxygen utilizes steroidal starting materials of the formula

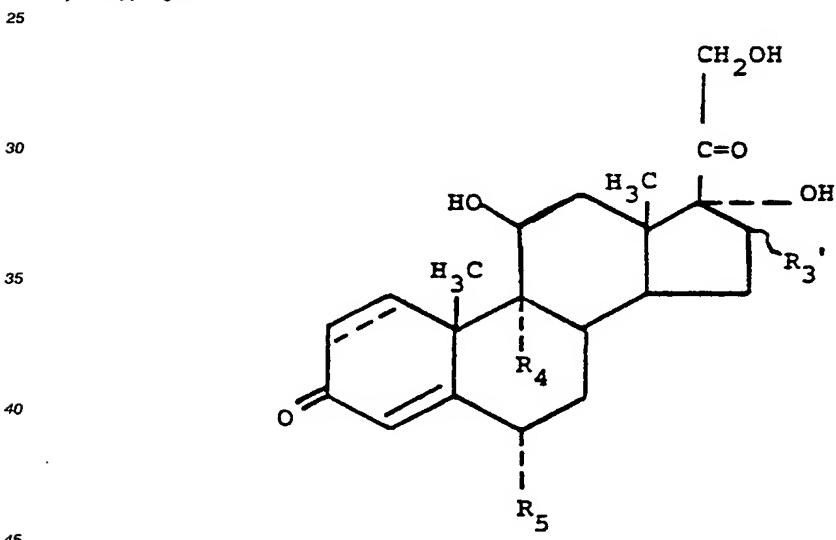
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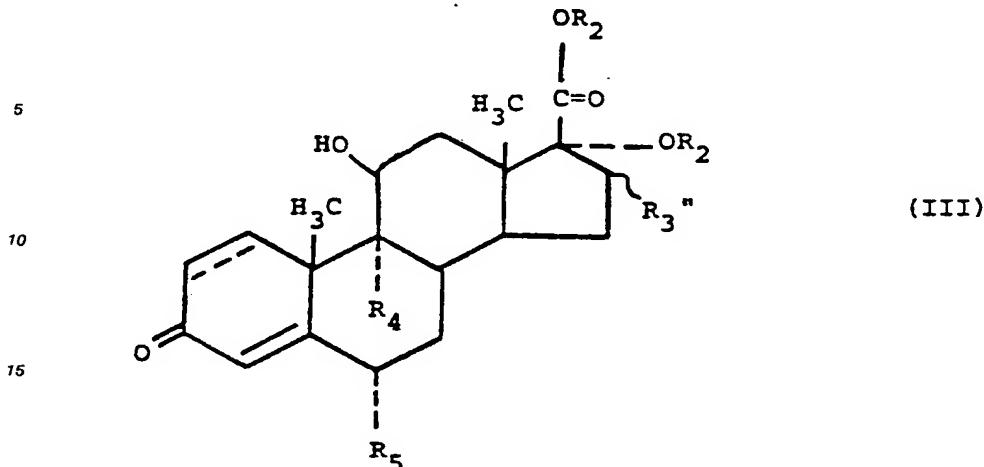
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wherein R₄, R₅ and the dotted line in ring A are defined as before and R_{3'} is hydrogen, α -methyl, β -methyl, α -OH, β -OH or =CH₂ (and which can be conveniently prepared by treatment of the corresponding 21-hydroxypregnolones of the formula:



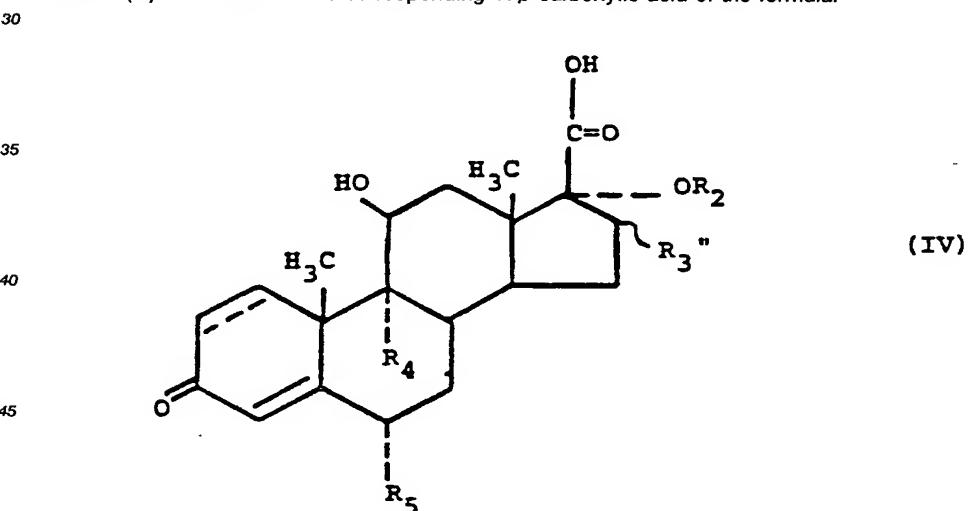
wherein R_{3'}, R₄, R₅ and the dotted line in ring A are defined as above with NaIO₄ in a suitable organic solvent at room or elevated temperature.) According to this process of the invention, a starting material of formula (II) is reacted with R₂I and KOH, wherein R₂ is defined as above, under anhydrous conditions, in an appropriate inert organic solvent such as dimethylsulfoxide (DMSO), dichloromethane, chloroform or tetrahydrofuran, preferably in the presence of a suitable acid acceptor (e.g., triethylamine, pyridine, calcium carbonate or other appropriate base). Time and temperature are not critical factors; however the reaction is conveniently carried out at a temperature between about 0°C and room temperature, for about 1 to 6 hours. The resultant novel 17 α -alkoxy 17 β -carboxylate has the formula:



wherein R₂, R₄, R₅ and the dotted line in the A ring are defined as above and R_{3''} is H, α -CH₃, β -CH₃, α -OR₂, β -OR₂ or =CH₂. When R_{3''} in the starting material of formula (II) is α -OH or β -OH, sufficient R₂I is generally employed to ensure formation of the alkoxy grouping at the 16-position as well as at the 17-position [i.e., when R_{3'} in formula (II) is OH, R_{3''} in the resultant intermediate of formula (III) is α - or β -OR₂].

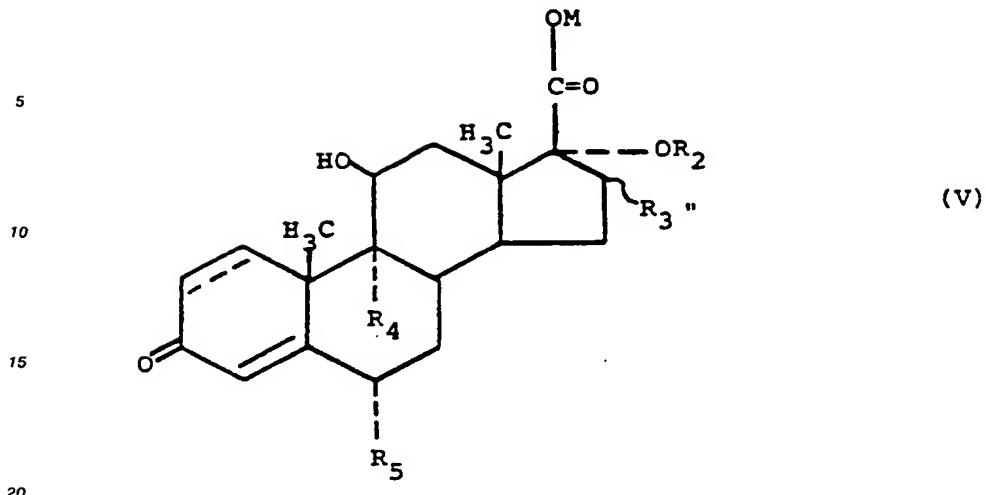
25 Sometimes, when a compound of formula (I) wherein R₂ contains a sulfinyl or sulfonyl grouping is desired, such a grouping is not introduced via the R₂I reaction, but is prepared from the corresponding thio-containing R₂ derivative at a later stage in the synthetic scheme, as will be discussed in more detail below.

After the above-described introduction of the 17 α - and 17 β -substituents, the resultant novel steroid of formula (III) is converted to its corresponding 17 β -carboxylic acid of the formula:



50 wherein R₂, R₄, R₅ and the dotted line in the A ring are defined as above and R_{3''} is H. The novel steroid (IV) is typically formed by reacting the steroid of (III) with KOH, under anhydrous conditions, in an appropriate inert organic solvent such as dimethylsulfoxide (DMSO), dichloromethane, chloroform or tetrahydrofuran.

55 After the above-described preparation of the novel steroid of formula (IV), the formula (IV) is converted to its corresponding metal salt of the formula:

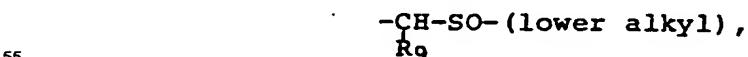


wherein R_2 , R_3'' , R_4 , R_5 and the dotted line in the ring A are defined as above, and M is a suitable metal, e.g., alkali metal (such as sodium or potassium), alkaline earth metal/2, or thallium or NH_4^+ . The novel salt of formula (V) is typically formed by reacting the steroid of formula (IV) with a hydroxide (MOH) or alkoxide (MOR) in an appropriate organic solvent, such as ethyl ether or tetrahydrofuran, at a temperature of $0^\circ C$ to room temperature, for 0.5 to 4 hours. Then, the salt of formula (V) is reacted with a compound of the formula $R_1\text{-}W$ wherein R_1 is defined as hereinabove and W is halogen, to afford the desired final product of formula (I). This step of the reaction sequence can be conveniently conducted at room temperature for about 1 to 24 hours, or at the boiling point of the solvent (i.e., acetonitrile, tetrahydrofuran, etc.) When it is desired to introduce a halosubstituted R_1 grouping into the steroid, e.g., when a compound of formula (I) wherein R_1 is chloromethyl is desired, it has been found that the reaction proceeds well using hexamethylphosphoramide as the solvent at lower temperatures (0 – $10^\circ C$) and employing a $R_1\text{-}W$ reactant wherein W is iodine (e.g., iodochloromethane). When a non-halogen containing R_1 grouping is desired (e.g., R_1 = alkyl or $-CH_2COOR_6$ where R_6 is alkyl, etc.), no such restrictions need be placed on the $R_1\text{-}W$ reactant or on the solvent; thus, W can be any halogen, preferably chloro or bromo, and the usual organic solvents such as dimethylformamide, dichloromethane, acetonitrile, tetrahydrofuran or chloroform can, if desired, be used instead of hexamethylphosphoramide. When a compound of formula (I) wherein R_1 contains a sulfinyl or sulfonyl grouping is desired, such a grouping is not generally introduced via the $R_1\text{-}W$ reaction, but is subsequently prepared from the corresponding thio steroid, as described below.

40 The compounds of formula (I) wherein R_1 (or R_2) is a sulfinyl- or sulfonyl-containing grouping can be prepared by oxidation of the corresponding thio steroids. Thus, for example, a compound of formula (I) wherein R_1 is



[wherein R_9 is H, lower alkyl, or combined with the lower alkyl group adjacent to S to form a cyclic system, as described hereinabove] can be reacted with 1 equivalent of m-chloroperoxybenzoic acid at 0 – $25^\circ C$ for 50 1 to 24 hours, in a suitable solvent such as chloroform, to afford the corresponding compound of formula (I) wherein R_1 is



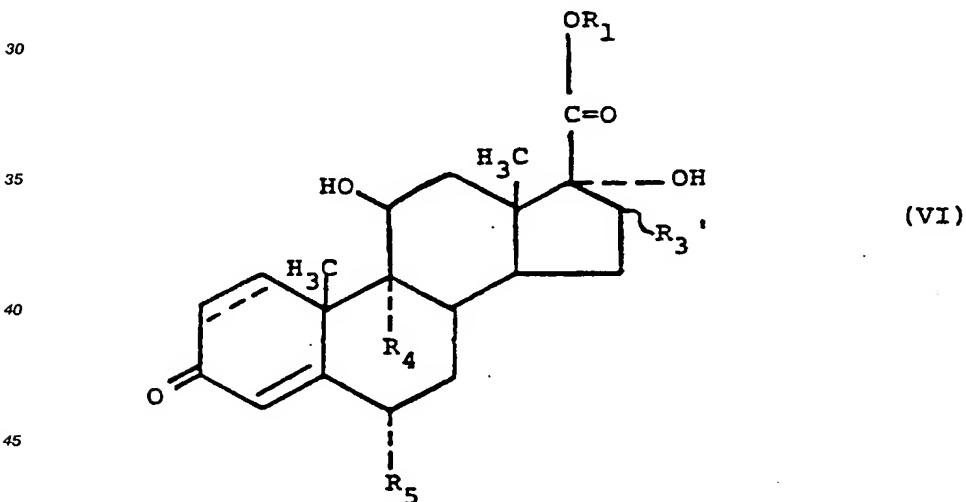
or with 2 equivalents of m-chloroperoxybenzoic acid to afford the corresponding compound of formula (I) wherein R_1 is



5 This type of reaction can also be utilized to prepare compounds of formula (I) wherein R_1 is $-\text{CH}_2\text{COOR}_6$ wherein R_6 is substituted alkyl, cycloalkyl, cycloalkenyl, alkenyl, phenyl, or benzyl, wherein the substituent is lower alkylsulfinyl or lower alkylsulfonyl, from the corresponding lower alkylthio-substituted formula (I) steroids; to prepare compounds of formula (I) wherein R_1 is lower alkylsulfinyl- or alkylsulfonyl-substituted phenyl or benzyl from the corresponding lower alkylthio-substituted formula (I) steroids; and to prepare compounds of formula (I) wherein R_2 is substituted alkyl, cycloalkyl, cycloalkenyl, alkenyl, phenyl or benzyl wherein the substituent is lower alkylsulfinyl or lower alkylsulfonyl, from the corresponding lower alkylthio-substituted formula (I) steroids.

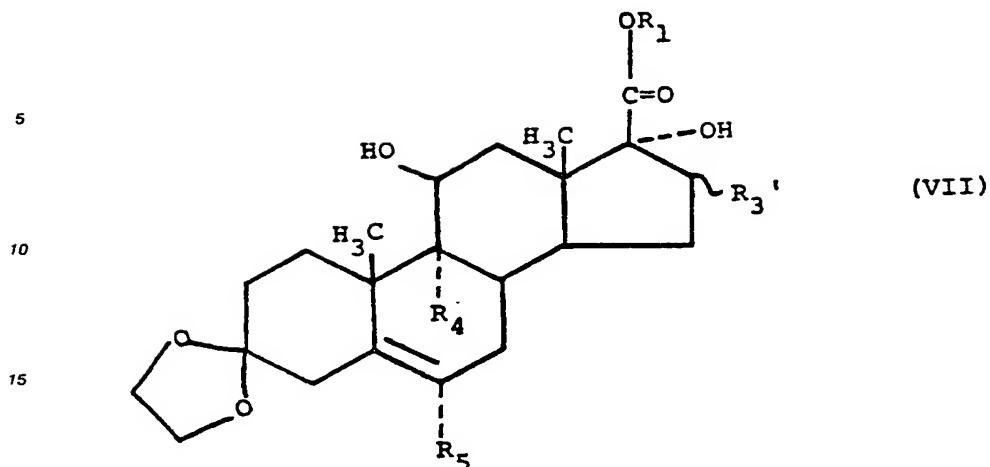
10 When the compounds of formula (I) wherein R_3 is α - or β -hydroxy are desired, same can be prepared by partial acid hydrolysis of the corresponding compounds of formula (I) wherein R_3 is α - or β - OR_2 , in a suitable solvent medium. Use of a mild reagent, e.g., oxalic acid in methanol, is desirable. Alternatively, 15 hydrolysis of the 16-alkoxy to the 16-hydroxy compound could be carried out at an earlier stage in any synthetic scheme described herein after the introduction of the 16,17 α -alkoxy, 17 β -carboxylate groupings, e.g., selective hydrolysis of an intermediate of formula (III) having 16 and 17 α -alkoxy groupings to the corresponding 16-hydroxy 17 α -alkoxy, followed by a two-step conversion to the corresponding compound of 20 formula (I) as described supra.

Another process for the preparation of the compounds formula (I) wherein Z is β -hydroxymethylene and X is oxygen utilizes the same 17 α -hydroxy-17 β -carboxylic acid starting materials of formula (II) as are employed in the synthetic scheme supra, but involves formation of the 17 β - COOR_1 grouping prior to 25 introduction of the 17 α - OR_2 substituent. Essentially, the same non-steroidal reactants, reaction conditions, etc., as described above are used for the introduction of each group. Thus, the starting material of formula (II) is first reacted with KOH in ROH to form the corresponding novel steroid of the formula:

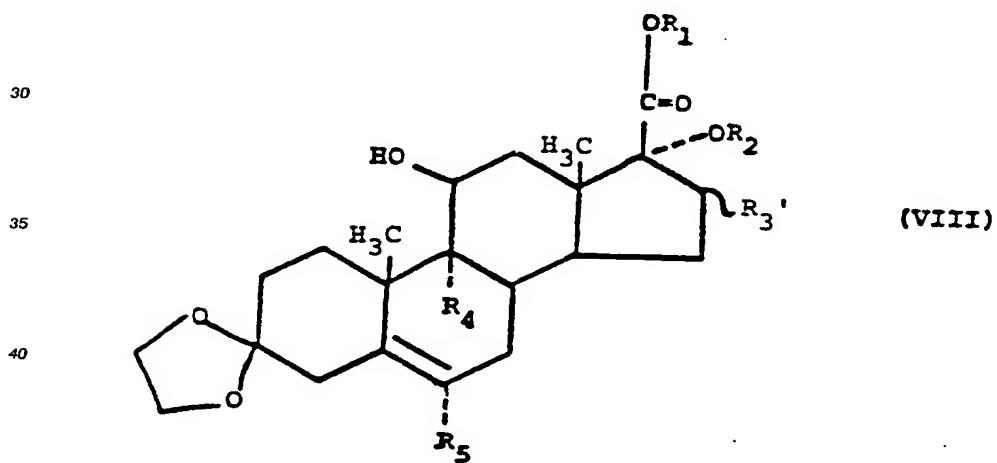


50 wherein R_1 , R_3' , R_4 , R_5 and the dotted line in ring A are defined as above, which is in turn reacted with R_2I wherein R_2 is defined above, to afford the corresponding 17 α -alkoxy-17 β -carboxylate of formula (I). Thus, again, when the starting material contains a 16-hydroxy group, the 16-alkoxy-17 β -carboxylate of formula (I) will be formed which can then be selectively hydrolyzed, if desired, to the corresponding 16-hydroxy-17 β -carboxylate of formula (I).

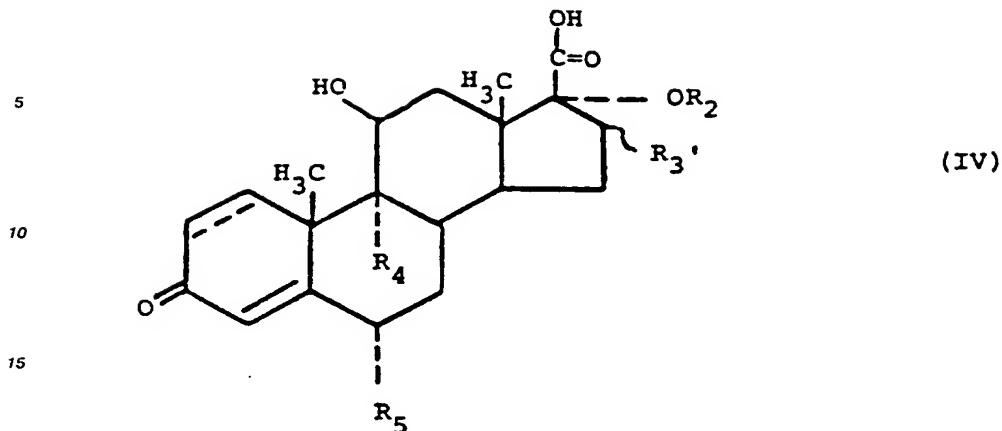
55 After the above-described introduction of the 17 β -carboxylate substituent, the resultant novel steroid of formula (VI) is converted to its corresponding 3-(1',3'-dioxacyclopent-2'-yl) of the formula:



25 After the above-described introduction of the heterocyclic group at the 3-position, the resultant novel steroid of formula (VII) is converted to its corresponding 17 α -alkoxy compound of the formula:

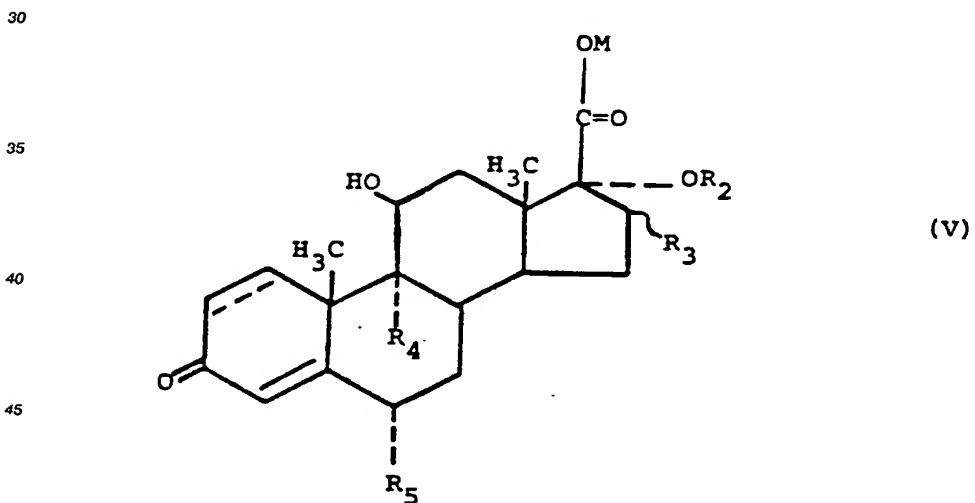


50 After the above-described introduction of the 17 α -alkoxy substituent, the resultant novel steroid of formula (VIII) is converted to the corresponding 3-oxo-17 β -carboxylic acid formula (IV) as previously described:

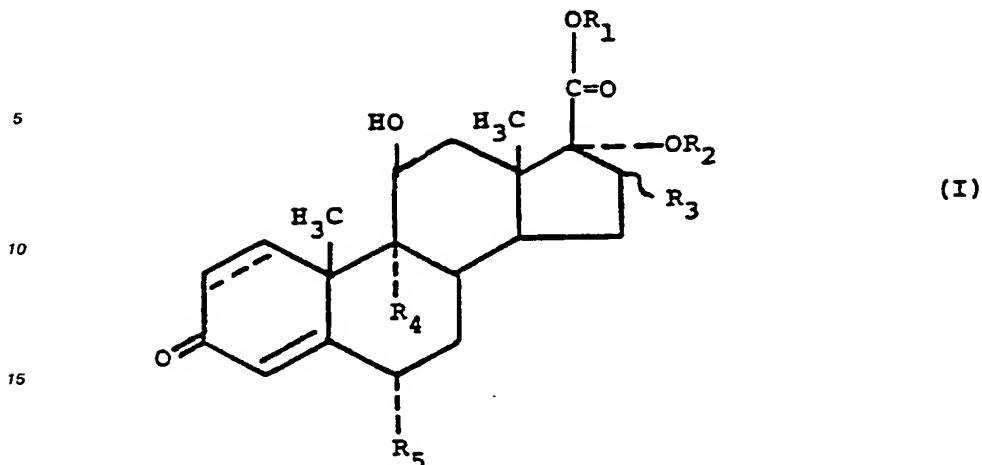


20 wherein R₂, R_{3'}, R₄, R₅ and the dotted line are defined as above and R_{3'} is H. The novel steroid of formula (IV) is typically formed by reacting the steroid of formula (VIII) with KOH, under anhydrous conditions, in an appropriate inert organic solvent such as dimethylsulfoxide, dichloromethane, chloroform or tetrahydrofuran. The reaction conditions used to convert III to IV are substantially the same as those used to convert VIII to IV.

25 After the above-described conversion of the 17beta-carboxylate to the 17beta-carboxylic acid moiety and conversion of the heterocyclic substituent to the oxo substituent at the 3-position, the resultant novel steroid of formula (IV) is reacted with MOH or MOR to form the corresponding intermediate of the formula (V) as previously described:



50 wherein R₂, R₃, R₄, R₅ and M and the dotted line in ring A are defined as above, which is then reacted with R₁W wherein R₁ and W are defined as above, to afford the corresponding 17beta-carboxylate of the formula:



20 wherein R₁, R₂, R₃, R₄, R₅ and the dotted line in ring A are as defined above. Thus, again, when the starting material contains a 16-hydroxy group, the 16-alkoxy-17 β -carboxylate of formula (I) will be formed which can then be selectively hydrolyzed, if desired, to the corresponding 16-hydroxy-17 β -carboxylate of formula (I). And, again, the compounds of formula (I) in which R₁ or R₂ is a sulfinyl- or sulfonyl-containing group can be conveniently prepared by oxidation of the corresponding thio-containing compounds of formula (I) as detailed hereinabove. Alternatively, the compounds of formula (I) wherein R₁ is a sulfinyl- or sulfonyl-containing group [e.g., when R₁ is

25

30 $-\text{CH}-\text{SO}-$ (lower alkyl)
R₉

or

35 $-\text{CH}-\text{SO}_2-$ (lower alkyl)
R₉

40 can be prepared by oxidation, preferably with m-chloroperoxybenzoic acid, of the corresponding compounds of formula (I) in which R₁ is a thio-containing group.

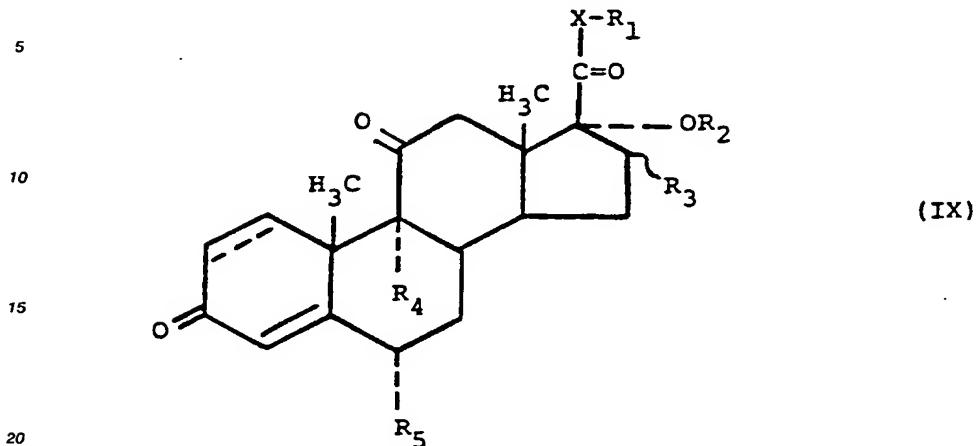
Other procedures for the preparation of selected compounds of formula (I) will be apparent to those skilled in the art. By way of example, a compound of formula (I) wherein R₁ or R₂ is halo-substituted can be subjected to a halogen exchange reaction in order to replace the halogen with a different halogen according to the order of reactivity Cl<Br<I. For example, reacting a chloroalkyl 17 β -carboxylate of formula (I) with an alkali metal iodide, e.g., sodium iodide, will afford the corresponding iodoalkyl 17 β -carboxylate. Similarly, a bromide salt (e.g., lithium bromide) can be reacted with a chloroalkyl 17 β -carboxylate to give the corresponding bromoalkyl 17 β -carboxylate. A suitable solvent for either reaction may be selected from the group consisting of hexamethylphosphoramide, acetone, ethanol, methyl ethyl ketone, dimethylacetamide, dimethylformamide and acetonitrile.

45

50 In like manner, a halogen exchange reaction based on relative solubilities can be used to convert a chloroalkyl 17 β -carboxylate or an iodoalkyl 17 β -carboxylate of formula (I) to the corresponding fluoroalkyl derivative. Silver fluoride can be employed in this reaction, which is conducted in a suitable organic solvent (e.g., acetonitrile), and which is especially useful in the preparation of the compounds in which R₁ is fluoromethyl or fluoroethyl.

55 The 21-hydroxypregnolones from which the steroidal starting materials of formula (II) are prepared can be obtained commercially or prepared by known methods. Likewise, the nonsteroidal starting materials used in the various processes discussed above are commercially available or can be prepared by known chemical procedures.

In yet another aspect, the present invention provides novel compounds of the formula:



wherein R₁, R₂, R₃, R₄, R₅, X and the dotted line in ring A are as defined with respect to formula (I) above. The 11-keto compounds of formula (IX) can be prepared by the procedures described hereinabove for the preparation of the corresponding 11 β -hydroxy compounds of formula (I). Thus, a starting material corresponding to formula (II) but having an 11-keto group is reacted with R₂I, to afford the corresponding novel intermediate corresponding to formula (III) but having an 11-keto group; that intermediate is then converted to the corresponding novel intermediate corresponding to formula (IV); that intermediate is then converted to its metal salt, which corresponds to formula (V) except for the presence of an 11-keto instead of an 11 β -hydroxy group; and the metal salt is then reacted with R₁W to afford corresponding compound of formula (IX). All reaction conditions are as previously described with respect to the corresponding processes for preparing the corresponding compounds of formula (I). Also, the preparation of the compounds of formula (IX), wherein R₁ is a sulfinyl- or sulfonyl-containing grouping or wherein R₃ is hydroxy generally proceeds as a final step in the synthetic scheme in a manner analogous to that used for the corresponding compounds of formula (I). Further, all of the above-described alternative processes for the preparation of the compounds of formula (I) are equally applicable to the preparation of the compounds of formula (IX) by simply substituting the 11-oxo starting material for the corresponding 11 β -hydroxy steroids used therein, e.g., replacing the 11-hydroxy group in formulas (VI), (VII) and (VIII) with an 11-oxo group and otherwise proceeding as described hereinabove for the reactions (II) \rightarrow (VI) \rightarrow (VII) \rightarrow (VIII) \rightarrow (IV) \rightarrow (V) \rightarrow (I).

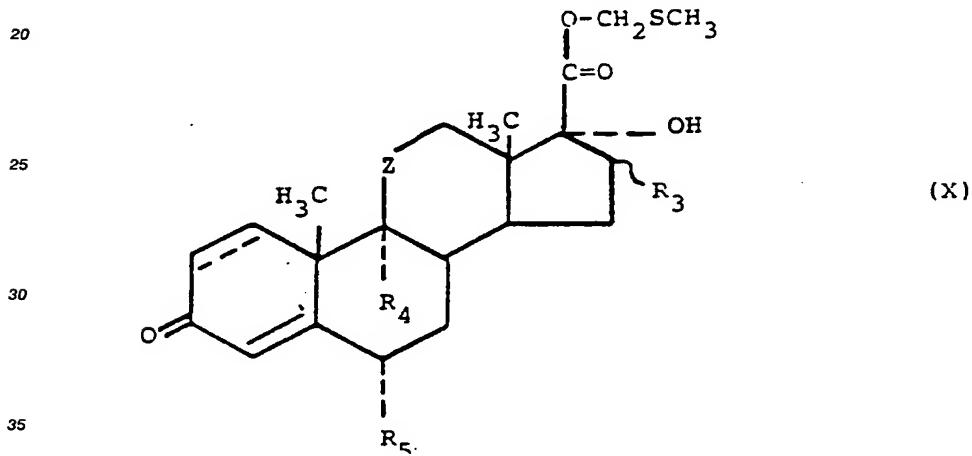
Also, the compounds of formula (IX) can be prepared by reacting the corresponding compounds of formula (I) with an oxidizing agent. The oxidation of a compound of formula (I) in order to convert it into the corresponding compound of formula (IX) is usually carried out by using an oxidizing agent in an appropriate solvent. The solvent may be any conventional solvent, for example, water, an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid), an alcohol (e.g. methanol, ethanol), a halogenated hydrocarbon (e.g. chloroform, dichloromethane), or the like. The oxidizing agent may also be any conventional agent which is effective for oxidizing a hydroxy group to a carbonyl group, for example, pyridinium chlorochromate, chromium trioxide in pyridine, hydrogen peroxide, dichromic acid, dichromates (e.g. sodium dichromate, potassium dichromate), permanganic acid, permanganates (e.g. sodium permanganate, potassium permanganate), or the like. The oxidizing agent is usually used in an amount of 1 mole or more, preferably 1 to 3 moles, per mole of the compound of formula (I). The reaction is usually carried out at a temperature of 0° to 40°C, preferably at about room temperature, for about 6 to 30 hours.

The novel compounds of formula (IX) are useful as soft steroid anti-inflammatory agents and also in vivo or in vitro precursors of the corresponding 11 β -hydroxy compounds. Thus, the compounds of formula (IX) can be reduced in vitro to afford the corresponding compounds of formula (I), using a reducing agent known to be capable of reducing the 11-oxo group to an 11 β -hydroxy group without modifying the remainder of the steroid starting material. Typically, microbiological reduction is advantageous for carrying out the desired conversion, although chemical reduction also is possible. Further, the compounds of formula (IX) may be formulated into appropriate dosage forms (e.g., retention enemas) for the treatment of conditions

such as ulcerative colitis. In such dosage forms, it is thought that the compounds of formula (IX) are microbiologically reduced by bacteria in the body (e.g. in the colon) to the highly active 11β -hydroxy steroids, which elicit the desired anti-inflammatory response.

The preferred compounds of formula (IX) are those which are precursors of the preferred compounds of formula (I) wherein Z is β -hydroxymethylene, namely corresponding 11-keto compounds of formula (IX). An especially preferred group of compounds of formula (IX) consists of those wherein X, R₁ and R₂ are defined as above with respect to formula (I) and the remaining structural variations are identical to those of cortisone (i.e. R₃, R₄ and R₅ are each a hydrogen atom and the 1,2-linkage is saturated), of prednisone (i.e. R₃, R₄ and R₅ are each hydrogen and the 1,2 - linkage is unsaturated), or of the 6 α - and/or 9 α -fluoro and the 16 α - or 16 β -methyl congeners thereof, particularly when R₁ and R₂ are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Most especially preferred of these derivatives are those wherein X is oxygen, R₂ is C₁-C₆ alkyl and R₁ is C₁-C₆ alkyl, C₁-C₆ (monohalo)alkyl [particularly chloromethyl] or -CH₂-Y-(C₁-C₆ alkyl) [particularly -CH₂-Y-CH₃].

Under oxidation conditions, it is important to protect the 11-hydroxy group when preparing the compounds of the present invention since it is known that the mixture of dimethylsulfoxide and acetic anhydride has oxidative properties with respect to primary and secondary alcohols. Therefore, it is possible to prepare a 17β -methylthiomethyl ether derivative having the formula

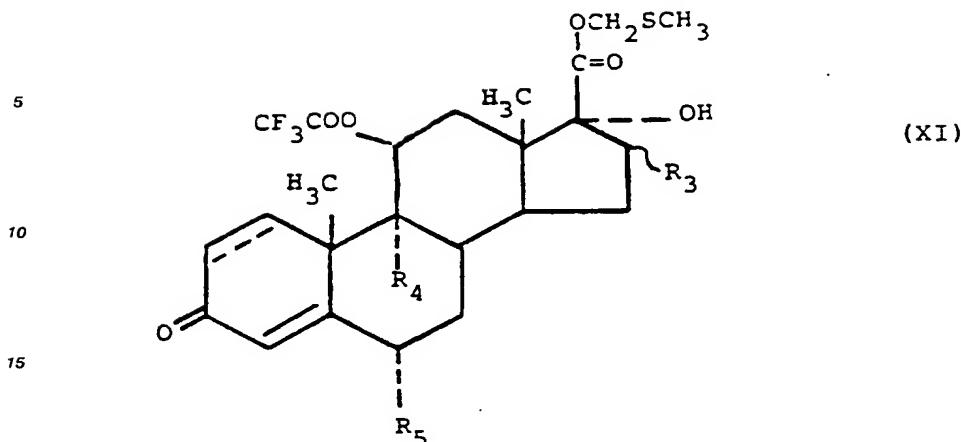


40 wherein R₃, R₄, R₅, Z and the dotted line in ring A are as previously defined, from the compound of formula (I) using triethylamine and chloromethylmethylsulfide (ClCH₂SCH₃). The methylthiomethyl ester of formula (X) is then treated with trifluoroacetic anhydride and pyridine at about -15°C to give mainly the desired 11 β -trifluoroacetate derivative having the formula

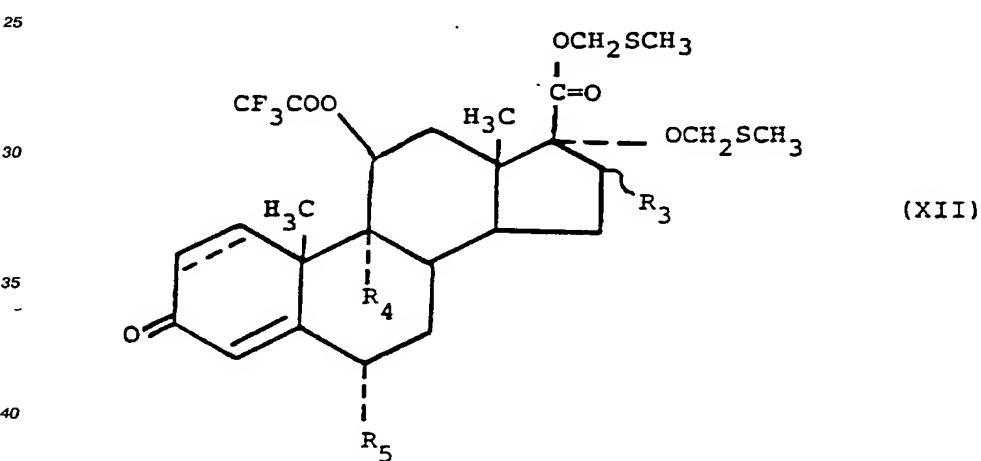
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wherein R₃, R₄, R₅ and the dotted line in ring A are as previously defined. The 11 β -trifluoroacetate of formula (XI) is then transformed to the 17 α -methylthiomethyl ester of formula (XII) using dimethyl sulfoxide and acetic anhydride under the same conditions as previously described.

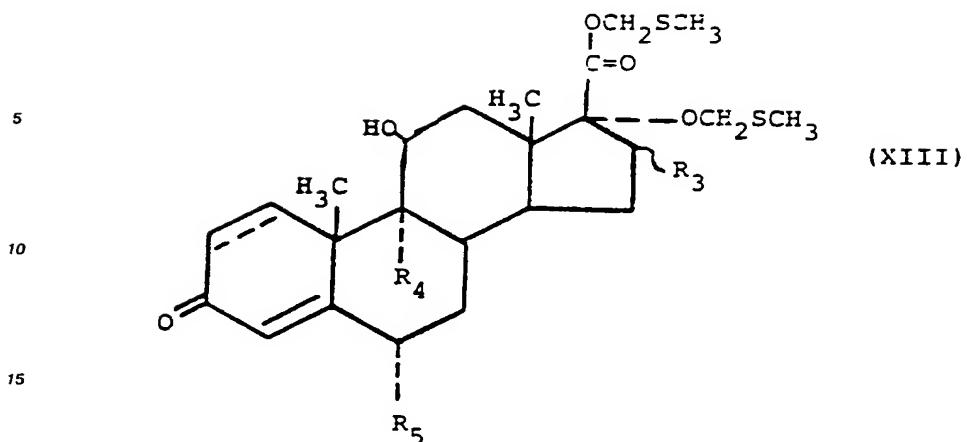


wherein R₃, R₄, R₅ and the dotted line in ring A are as previously defined.

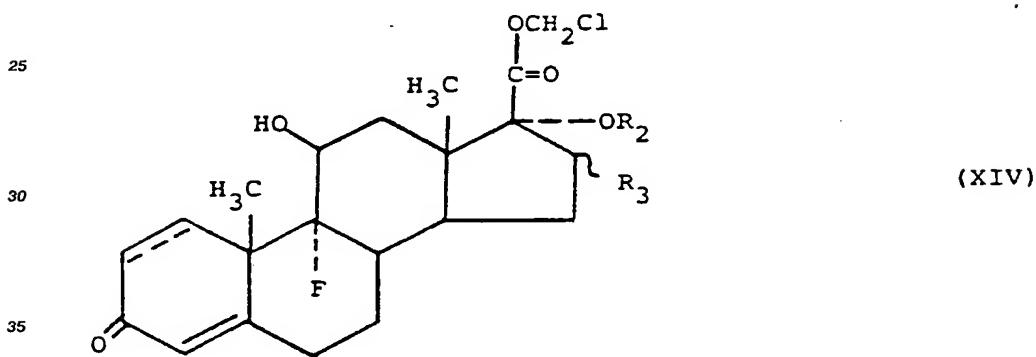
45 The compound of formula (XII) is then reacted with triethylamine and methanol in a sodium bicarbonate and water solution to form a compound having the formula

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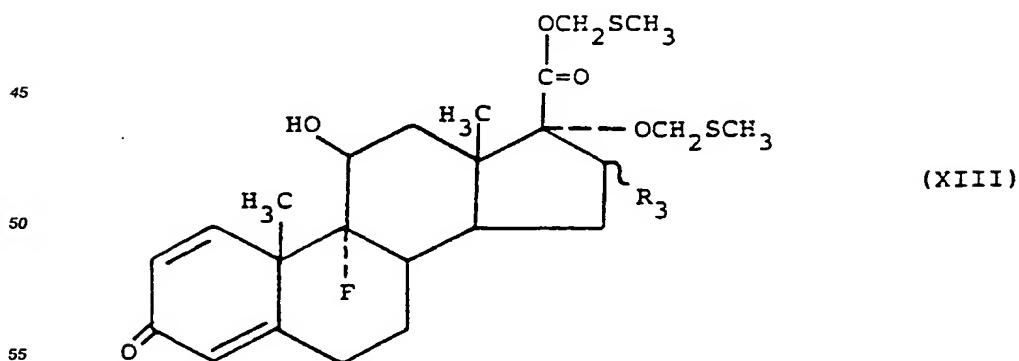
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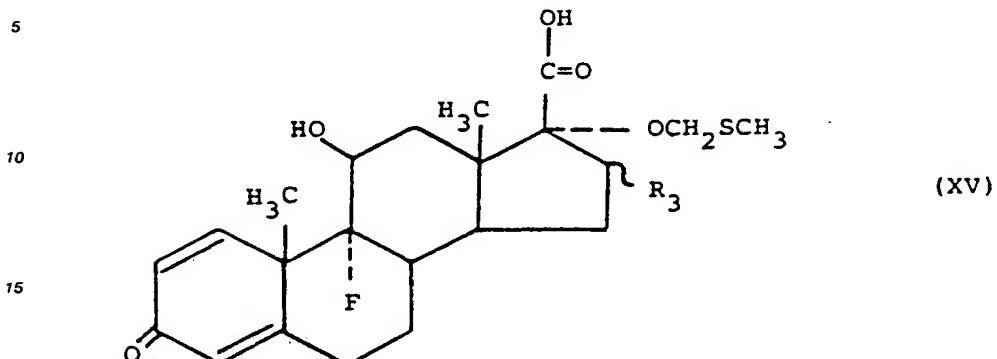
20 wherein R₃, R₄, R₅ and the dotted line in ring A are as previously defined.
 Dexamethasone-type compounds having the structure:



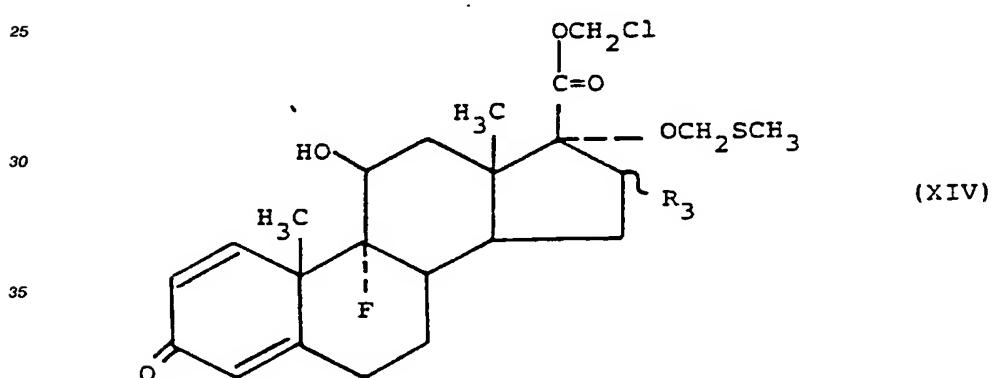
40 may be prepared in a manner well-known to those of average skill in the art. For instance, a suitable starting material may be



wherein R₃ is as previously defined. The compound of formula (XIII) is reacted with KOH in methanol and the potassium salt of tertiary butyl hydroxide in tetrahydrofuran. The novel steroid formed has the formula:



20 wherein R₃ is as previously defined. The resultant novel steroid of formula (XV) is then converted to its corresponding chloromethyl ester of the formula:



40 wherein R₃ is as previously defined. The novel steroid (XIV) is typically formed by reacting the steroid of (XV) with KOH and chloromethylmethyl chlorosulfate (CICH₂S₂O₂Cl) under phase transfer conditions. The article "Chlorosulfates as Reagents in the Synthesis of Carboxylic Acid Esters Under Phase-Transfer Conditions" by Binderup E. and Hansen E.T., in Synthetic Communications, 14(9), 857-864 (1984) discloses 45 the use of chloromethyl chlorosulfate in the synthesis of chloromethyl esters of sensitive carboxylic acids under phase transfer conditions, which synthesis is applicable hereto.

The results of various activity studies of representative species of the invention, discussed in detail below, clearly indicate the potent anti-inflammatory activity and the minimal systemic activity toxicity of the soft steroids of formula (I). In view of this desirable separation of local and systemic activities, the compounds of the invention can be used in the treatment of topical or other localized inflammatory conditions without causing the serious systemic side effects typically exhibited by the known natural and synthetic glucocorticosteroids such as cortisone, hydrocortisone, hydrocortisone, 17 α -butyrate, betamethasone 17-valerate, triamcinolone, betamethasone dipropionate and the like.

55 TOPICAL VASOCONSTRICITION TEST

A topical vasoconstriction test was conducted using the general method of McKenzie, A.W. and R.B. Stoughton, Arch. Dermatol. 86, (1962), 608-10. The topical vasoconstriction test was done in order to

evaluate the anti-inflammatory potency of the novel compounds of the present invention. A 0.03M solution of the test compound in acetone/isopropylmyristate 90:10 volume/volume was prepared. An aliquot of 0.05 milliliter was applied to a circular patch, one centimeter in diameter, which was in turn applied against the skin of the flexor surface of the forearm (previously cleansed with ethanol 95% and dried). This application
 5 was occluded with a water-impervious film. The patch was removed after about six hours and the blanching score was evaluated one hour later. Two control compounds were used at the same time and under the same conditions. The control compounds were hydrocortisone 17-valerate and corticic acid 17-ethylcarbonate chloromethylester. The experiment was made in duplicate and the average estimation values for the blanching activity are reported in Table I. The left column of Table I indicates the 17 α -substituent of the
 10 structure:

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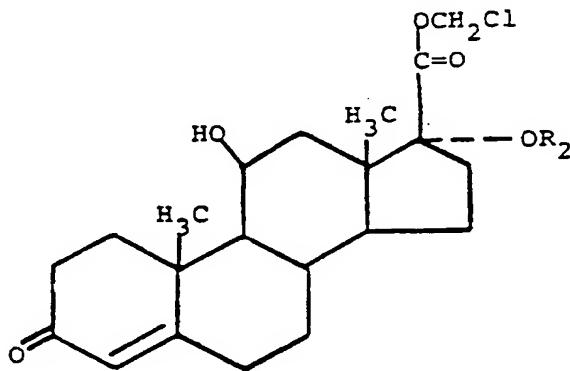


TABLE I

30

35

40

BLANCHING STUDIES	
17 α -substituent	Value
-OCH ₃ *	--
-OCH ₂ H ₅ **	0.75
-OC ₃ H ₇ **	1 **
-OC ₄ H ₉	0.5
valerate	1.5
carbonate	1.75

* The 17-methoxy homologue was determined in a previous study to have low activity.

** Simple study - duplicate experiment not conducted.

45

50

55

The compounds of formula (I) can be combined with suitable non-toxic pharmaceutically acceptable carriers to provide pharmaceutical compositions for use in the treatment of topical or other localized inflammation. Obviously, in view of their lack of systemic activity, the compounds of the present invention are not intended for treatment of conditions where systemic adrenocortical therapy is indicated, e.g., adrenocortical insufficiency. As examples of inflammatory conditions which can be treated with pharmaceutical compositions containing at least one compound of the invention and one or more pharmaceutical carriers, the following can be mentioned: dermatological disorders such as atopic dermatitis, acne, psoriasis or contact dermatitis; allergic states such as bronchial asthma; ophthalmic and otic diseases involving acute and chronic allergic and inflammatory reactions; respiratory diseases; ulcerative colitis; and anorectal inflammation, pruritus and pain associated with hemorrhoids, proctitis, cryptitis, fissures, postoperative pain and pruritus ani. Such compositions may also be applied locally as a prophylactic measure against the inflammation and tissue rejection which arise in connection with transplants.

Obviously, the choice of carrier(s) and dosage forms will vary with the particular condition for which the composition is to be administered.

Examples of various types of preparations for topical/local administration include ointments, lotions, creams, powders, drops, (e.g. eye or ear drops), sprays, (e.g. for the nose or throat), suppositories, retention enemas, chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) and aerosols. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or glycols. Such base may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a glycolic solvent such as propylene glycol or 1,3-butanediol. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, polyethylene glycols, woolfat, hydrogenated lanolin and beeswax and/or glyceryl monostearate and/or non-ionic emulsifying agents.

10 The solubility of the steroid in the ointment or cream may be enhanced by incorporation of an aromatic alcohol such as benzyl alcohol, phenylethyl alcohol or phenoxyethyl alcohol.

15 Lotions may be formulated with an aqueous or oily base and will in general also include one or more of the following, namely, emulsifying agents, dispersing agents, suspending agents, thickening agents, solvents, coloring agents and perfumes. Powders may be formed with the aid of any suitable base, e.g., talc, lactose or starch. Drops may be formulated with an aqueous base also comprising one or more dispersing agents, suspending agents or solubilizing agents, etc. Spray compositions may, for example, be formulated as aerosols with the use of a suitable propellant, e.g. dichlorodifluoromethane or trichlorofluoromethane.

20 The proportion of active ingredient in the compositions according to the invention will vary with the precise compound used, the type of formulation prepared and the particular condition for which the composition is to be administered. The formulation will generally contain from about 0.0001 to about 5.0% by weight of the compound of formula (I). Topical preparations will generally contain 0.0001 to 2.5%, preferably 0.01 to 0.5%, and will be administered once daily, or as needed. Also, generally speaking, the 25 compounds of the invention can be incorporated into topical and other local compositions formulated substantially as are such presently available types of compositions containing known glucocorticosteroids, at approximately the same (or in the case of the most potent compounds of the invention, at proportionately lower) dosage levels as compared to known highly active agents such as methyl prednisolone acetate and beclomethasone dipropionate or at considerably lower dosage levels as compared to less active known 30 agents such as hydrocortisone.

35 Thus, for example, an inhalation formulation suitable for use in the treatment of asthma can be prepared as a metered-dose aerosol unit containing a representative species of the invention such as chloromethyl 17 α -methoxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, according to procedures well-known to those skilled in the art of pharmaceutical formulations. Such an aerosol unit may contain a microcrystalline suspension of the aforementioned compound in suitable propellants (e.g., trichlorofluoromethane and dichlorodifluoromethane), with oleic acid or other suitable dispersing agent. Each unit typically contains 10 milligrams of the aforesaid active ingredient, approximately 50 micrograms of which are released at each actuation. When one of the more potent species of the invention, e.g. chloromethyl 17 α -methoxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate, is employed, each unit typically contains 40 1 milligram of the active ingredient and releases approximately 5 micrograms at each actuation.

45 Another example of a pharmaceutical composition according to the invention is a foam suitable for treatment of a wide variety of inflammatory anorectal disorders, to be applied anally or perianally, comprising 0.1% of a compound of formula (I) such as chloromethyl 17 α -ethoxy-11 β -hydroxyandrost-4-en-3-one 17 β -carboxylate, and 1% of a local anaesthetic such as pramoxine hydrochloride, in a mucoadhesive foam base of propylene glycol, ethoxylated stearyl alcohol, polyoxyethylene-IO-stearyl ether, cetyl alcohol, methyl paraben, propyl paraben, triethanolamine, and water, with inert propellents. When a more potent compound of the invention is employed, a less active ingredient generally is used, e.g. 0.05% of chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -methoxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate.

50 Yet another pharmaceutical formulation according to the invention is a solution or suspension suitable for use as a retention enema, a single dose of which typically contains 40 milligrams of a compound of the invention such as chloromethyl 17 α -ethoxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate (or 20 milligrams of a more potent compound of the invention such as chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate or chloromethyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-17 α -propoxy androsta-1,4-dien-3-one-17 β -carboxylate) together with sodium chloride, polysorbate 80 and from 1 to 6 ounces of water (the water being added shortly before use). The suspension can be administered as a 55 retention enema or by continuous drip several times weekly in the treatment of ulcerative colitis.

Other pharmaceutical formulations according to the invention are illustrated in the examples which follow.

Without further elaboration, it is believed that one of ordinary skill in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the following examples are to be construed as merely illustrative and not limitative of the remainder of the specification and claims in any way whatsoever.

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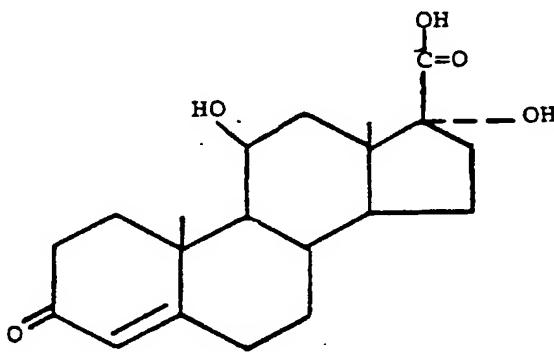
EXAMPLE 1

To a solution of hydrocortisone (15 grams, 0.04 mol) in 120 milliliters of tetrahydrofuran and 30 milliliters of methanol at room temperature is added a warm (approximately 50°C) solution of sodium metaperiodate (25.7 grams, 0.12 mol) in 100 milliliters of water. The reaction mixture is stirred at room temperature for 2 hours, then is concentrated under reduced pressure to remove the tetrahydrofuran and methanol. The solid is triturated with 50 milliliters of water, separated by filtration, washed with water and dried in *vacuo* at 50°C for 3 hours. The product, 11 β ,17 α -dihydroxyandrost-4-en-3-one 17 β -carboxylic acid (i.e., cortienic acid), melts at 231-234°C, is obtained in approximately 96% yield (13.76 grams), and can be represented by the structural formula

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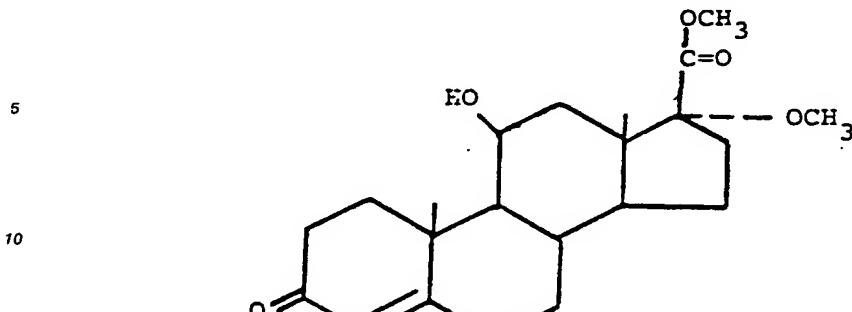
EXAMPLE 2

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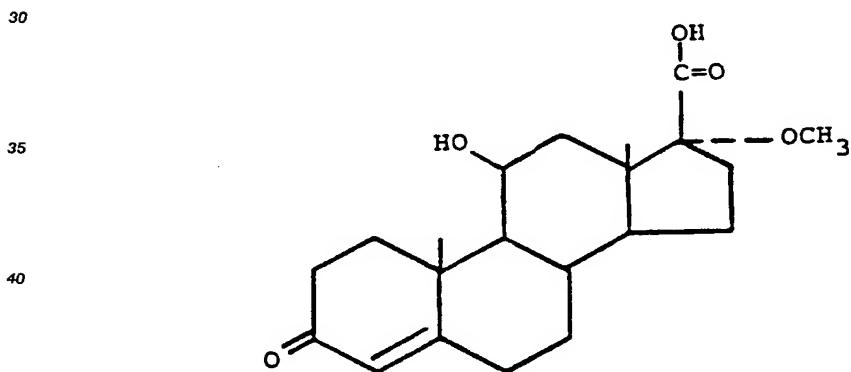
To a solution of powdered potassium hydroxide (2.14 grams) in dimethylsulfoxide (10 milliliters) was added 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylic acid (1.7 gram; 4.88 millimoles). The mixture was stirred for five minutes and immediately followed by addition of methyl iodide (1.22 milliliters; 19.5 millimoles). After stirring for one hour and fifteen minutes at 25°C, the mixture was diluted with 100 ml of ethyl acetate. The mixture was then washed successively with 10 milliliters water, 10 milliliters Na₂S₂O₃ (5% weight/volume), 10 milliliters NaHCO₃ (5% weight/volume) and then three additional times with 10 milliliters water. The organic solution was then dried over MgSO₄ and evaporated under partial pressure. The white crystalline crude product weighed 1.73 gram (94% theoretical) and had a melting point of 195°C to 201°C. Crystallization from CH₂C₂/Pentane raised the melting point to 215°C to 217°C then 217°C to 218.5°C. Elemental analysis: Required C70.18; H8.57; Found C70.16; H8.62. I.R. (KBr) 3500, 1725, 1655, 1210, CM⁻², H nmr (CDCl₃): 0.93 (S, 3, 18CH₃); 1.43 (S, 3, 19CH₃); 3.10 (S, 3, 170CH₃); 5:65 (S, 1, C=CH). The product, methyl 11 β -hydroxy-17 α -methoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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EXAMPLE 3

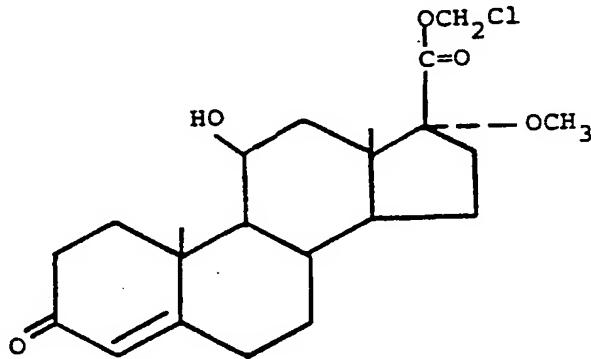
20 The methyl 11β-hydroxy-17α-methoxyandrost-4-en-3-one-17β-carboxylate (3.76 grams; 10 millimoles) was stirred overnight (16 hours) at 50 °C, under nitrogen in a mixture of powdered potassium hydroxide (4.50 grams) in 15 milliliters dimethylsulfoxide. The reaction mixture was then diluted with 200 milliliters water, acidified with dilute HCl, stirred 30 minutes and extracted with several portions of ethylacetate. The organic layer was then washed with 30 milliliters water, evaporated and taken up into 150 milliliters NaHCO₃ solution (5% weight/volume). The aqueous solution was then washed with 30 milliliters methylene chloride, acidified 25 with diluted HCl, filtered, and the residue was dried *in vacuo* at 40 °C overnight. The crude, yellow, pseudocrystalline product, 11β-hydroxy-17α-methoxyandrost-4-en-3-one-17β-carboxylic acid, weighed 3.05 grams (84% theoretical) ¹H nmr (DMSO_δ): 0.92 (S,3,18CH₃); 1.38 (S,3,19CH₃); 3.04 (S,3,0CH₃); 5.50 (S,1,C=CH); 8.28 (S,<I,COOH). The product can be represented by the structural formula

EXAMPLE 4

50 A 1 normal solution of KOH (3.62 milligrams; 1 millimole) in methanol was added dropwise to the 11β-hydroxy-17α-methoxyandrost-4-en-3-one-17β-carboxylic acid at 0 °C in an ice bath. The solution was evaporated under *vacuo* and dried thoroughly. The resulting potassium salt was mixed with 10 milliliters dimethylsulfoxide and 4 millimoles chloroiodomethane. After stirring for seven hours at room temperature (24 °C), the mixture contained a precipitate of potassium iodide. The mixture was then diluted with 100 milliliters ethylacetate and washed successively with 18 milliliters water, 10 milliliters Na₂S₂O₃ (5% weight/volume), 10 milliliters NaHCO₃ and three times with 10 milliliters water. The product was dried over MgSO₄ and evaporated under partial pressure. The dried product was purified by column chromatography from 12 grams of Silica gel (100-200 mesh type 60A special), eluted with EtOAc/CHCl₃ 20:80 and crystallized from ethylacetate/ether to give a final product that melted at 195 °C-196 °C and ¹H nmr (CDCl₃):

0.95 (S,3,18CH₃); 1.43 (S,3,19CH₃) 3.12 (S,3,0CH₃); 5.60 (S,I,C=CH); 5.75 (S,2,COOCH₂Cl). IR (KBr): 3400, 1755, 1655, 1205, 1110 (ether) cm⁻¹. Elemental analysis: Required: C64.30; H7.60; C18.63; Found: C64.16; H7.63; C18.63. The product, chloromethyl 11 β -hydroxy-17 α -methoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

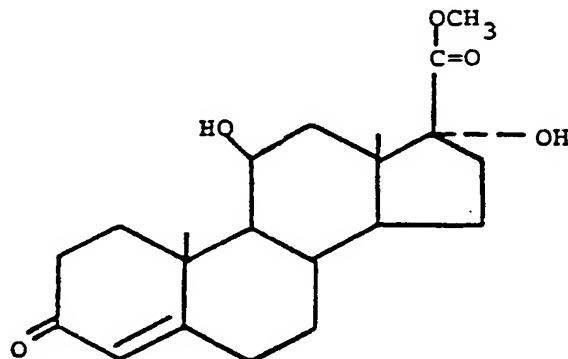
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EXAMPLE 5

25 11 β , 17 α -Dihydroxyandrost-4-en-3-one-17 β -carboxylic acid (3.484 grams; 10 millimoles) was dissolved into methylalcohol. A 10 milliliter solution of 1 normal KOH in methanol was added dropwise to the cold mixture. The solution was evaporated under vacuo and the residue was dried thoroughly and taken up into 20 milliliters dimethylsulfoxide and 2.5 milliliters methyl iodide (48 millimoles). After stirring overnight at room temperature, the mixture was diluted with 150 milliliters ethylacetate and washed successively with 50 milliliters NaHCO₃ (3% weight/volume), 50 milliliters Na₂S₂O₃ (5% weight/volume) and three additional times with 50 milliliters water. The mixture was dried over MgSO₄ and evaporated. The product crystallized from the ethylacetate, and 3 crops gave 3.31 grams (92%) of white crystals melting at 206 °C to 207 °C (little at 207 °C to 208 °C). ¹H nmr (CDCl₃): 0.98 (S,3,18CH₃); 1.45 (S,3,19CH₃); 3.75 (S,3,COOCH₃); 5.67 (S,I,C=CH). The product, methyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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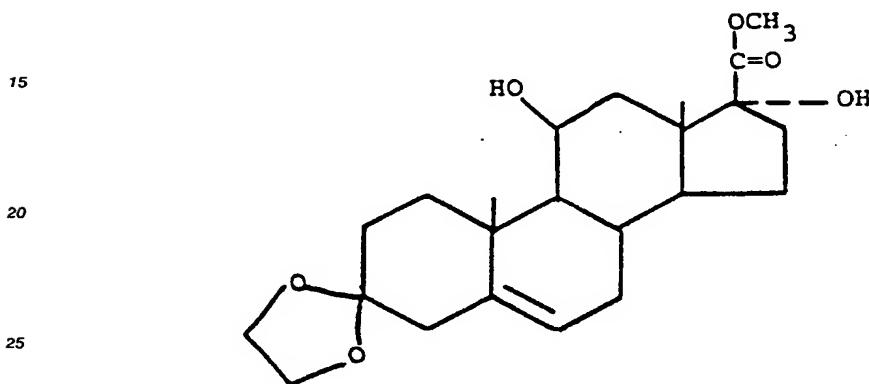


EXAMPLE 6

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The methyl 11 β -17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate (10.332 grams; 22.5 millimoles) was taken into 178 milliliters of ethylene glycol, then 85 milligrams of p-toluenesulfonic acid (anhydrous, crystallized from benzene) was added. The solvent was slowly distilled off at 0.3-1 mm Hg for two hours.

The distillation head was 60°C to 70°C and the mixture turned red after about 30 minutes when the compound started to precipitate. The suspension was neutralized with NaHCO₃ (the mixture turned colorless), then the suspension was poured into 200 milliliters of cold water and stirred for at least 30 minutes. The white precipitate was isolated by filtration, washed with water and dried in a freeze dryer. Thin 5 layer chromatography showed a small amount of starting material and a few percent of a product that was identified as the Δ9,11 3,3' cyclic ketal. Triturating the product with a few milliliters of ether yielded white crystals of melting point 204°C to 205°C that had satisfactory elemental analysis. Required: C67.96; H8.43; Found: C67.71; H8.47. ¹H nmr (CDCl₃): 0.93 (S,3,18CH₃); 1.27 (S,3,19CH₃) 3.70 (S,3,COOCH₃); 3.90 (S,4,0CH₂CH₂O); 5.12 (S,1,C=CH). The product, ¹⁵methyl 11 β ,17 α -dihydroxyandrost-5-en-3-(1',3'-10 dioxacyclopent-2'-yl)-17 β -carboxylate, can be represented by the structural formula:



30 EXAMPLE 7

Powdered KOH (1.2 grams) was stirred 5 minutes into 15 milliliters dimethylsulfoxide, then 2.15 grams methyl 11 β ,17 α -dihydroxyandrost-5-en-3-(1',3'-dioxacyclopent-2'-yl)-17 β -carboxylate (5.3 millimoles) was added. This was immediately followed by the addition of 1.7 milliliters iodoethane (21.2 millimoles) and the 35 mixture was stirred at 25°C for 23 hours. The reaction mixture was then diluted with 158 milliliters ethylacetate and washed successively with 50 milliliters Na₂S₂O₃ (5% weight/volume), and three times with 50 milliliters water. The mixture was then dried over MgSO₄ and evaporated to give 1.92 grams of a crude product (83% theoretical). Some product had been extracted in the aqueous phase and was identified as cortenic acid-3,3'cyclic ketal. Purification from 45 grams of silica gel, eluting with benzene/EtOAc 80:20 40 yielded 1.1 gram of a white compound. IR (KBr): 3500, 1725, 1215, 1110, 1085 cm⁻¹. ¹H nmr 0.90 (S,3,18CH₃); 1.10 (T,3,J=7Hz,OCH₂CH₃); 1.28 (S,3,19CH₃); 3.32 (M,2,0CH₂CH₃) 3.70 (S,3,COOCH₃); 3.95 (S,4,0CH₂CH₂O); 5.15(S,1,C=CH). The product, ¹⁵methyl 11 β -hydroxy-17 α -ethoxyandrost-5-en-3-(1',3'-dioxacyclopent-2'-yl)-17 β -carboxylate, can be represented by the structural formula:

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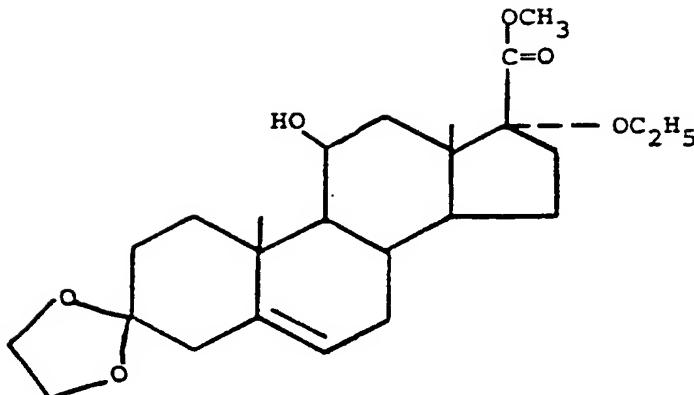
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Substitution of an equivalent quantity of iodopropane for iodoethane employed above and substantial repetition of the foregoing procedure afforded methyl 11 β -hydroxy-17 α -propoxy-androst-4-en-3-(1',3'-dioxacyclopent-2'-yl)-17 β -carboxylate, having an identical H nmr spectrum to that presented above without the triplet of 1.10 ppm.

Substitution of bromobutane for iodoethane at a ratio of 4 parts bromobutane per part methyl 11 β ,17 α -dihydroxyandrost-5-en-3-(1',3'-dioxacyclopent-2'-yl)-17 β -carboxylate and substantial repetition of the foregoing procedure while allowing the reaction to proceed for three days afforded methyl 11 β -hydroxy-17 α -butoxyandrost-5-en-3-(1',3'-dioxacyclopent-2'-yl)-17 β -carboxylate. The crude product was a mixture of the methyl and butyl ester.

EXAMPLE 8

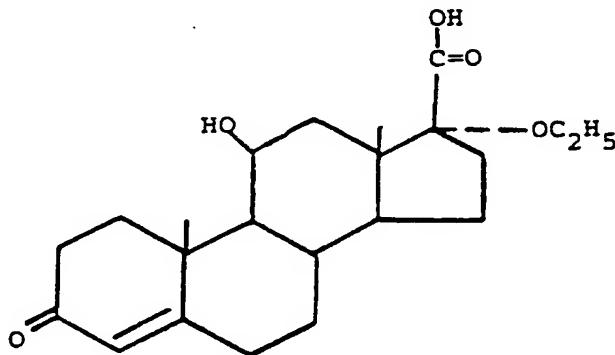
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The methyl 11 β -hydroxy-17 α -ethoxyandrost-4-en-3(1',3'-dioxacyclopent-2'-yl)-17 β -carboxylate (1.1 grams, 2.5 millimoles), the first product described in Example 7, was stirred for 17 hours under nitrogen at 60 °C in 5 milliliters dimethyl sulfoxide containing 0.5 grams of powdered KOH. The reaction was then taken up into 150 milliliters of water, acidified slowly with dilute HCl to pH 1.2, stirred for fifteen minutes and extracted four times with 80 milliliters EtOAc. The mixture was dried over MgSO₄ and evaporated. The crude product was dissolved in NaHCO₃ (3% weight/volume), washed with EtOAc and acidified. Drying gave 669 milligrams (64%) of acid (11). IR (KBr): 3500, 1715, 1670, 1085 cm⁻¹. H nmr (DMSO_d₆): 0.92 (S,3,18CH₃); 1.05 (T,3,J=7Hz,OCH₂CH₃); 1.37 (S,3,19CH₃); 3.28 (M,2,0CH₂CH₃); 5.55 (S,I,C=CH). The product, 11 β -hydroxy-17 α -ethoxyandrost-4-en-3-one-17 β -carboxylic acid, can be represented by the structural formula:

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Likewise, the second and third products described in Example 7 were subjected to substantially the same procedure described above. The products obtained were 11β -hydroxy- 17α -propoxyandrost-4-en-3-one- 17β -carboxylic acid and 11β -hydroxy- 17α -butoxyandrost-4-en-3-one- 17β -carboxylic acid, respectively.

5 EXAMPLE 9

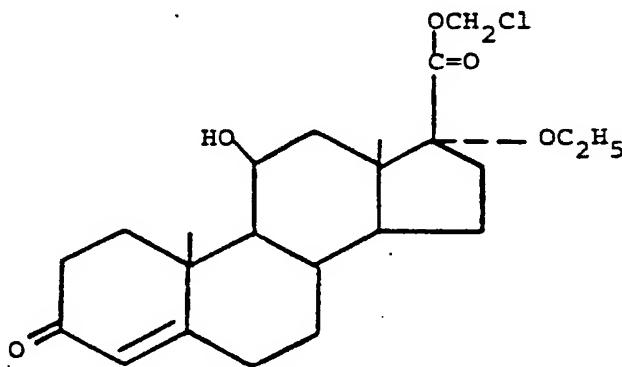
The potassium salt of the first product of Example 8, 11β -hydroxy- 17α -ethoxyandrost-4-en-3-one- 17β -carboxylic acid (1.58 millimole) was prepared in substantially the same manner as the potassium salt of Example 4. That is, the first product of Example 8 was stirred at room temperature for eight hours in 10 milliliters dimethylsulfoxide containing 1.25 milliliters chloriodomethane. The work-up described in Example 4 was followed and 0.594 gram of a crude product was obtained that was chromatographed on 15 grams silica gel, eluting with hexane/EtOAc 80:20 then 70:30. Crystallization from CH_2Cl_2 /Pentane gave white crystals melting at 203°C to 205°C . IR (KBr): 3400, 1750, 1650, 1205, 1110, 1060 cm^{-1} . H nmr (CDCl_3): 0.95 (S,3,18 CH_3); 1.13 (T,3,J=7 Hz , OCH_2CH_3); 1.43 (S,3,19 CH_3); 3.38 (M,2, OCH_2CH_3); 5.65 (S,1,C=H); 5.77 (S,2,COOCH₂Cl). Elemental analysis: Required: C65.08; H7.83; C18.34. Found: C64.86; H7.84; C18.32. The product, chloromethyl 11β -hydroxy- 17α -ethoxyandrost-4-en-3-one- 17β -carboxylate, can be represented by the structural formula:

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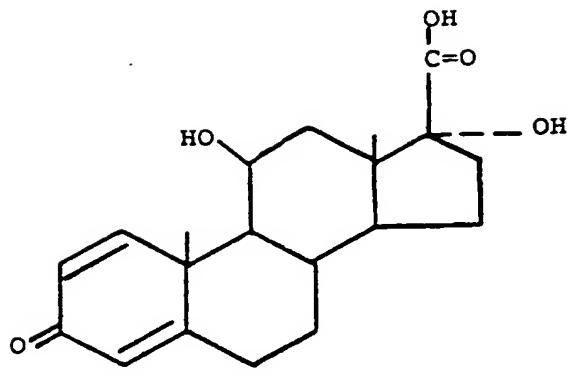
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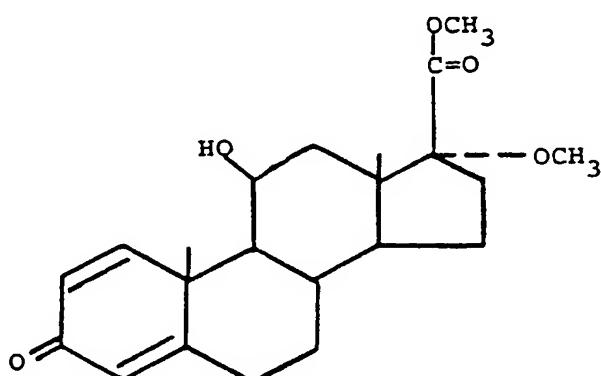
Example 10

Methoxy $11\beta,17\alpha$ -dihydroxy-1,4-diene-3-one- 17β -carboxylate (prednisolone) (30 grams; 0.08 moles) was placed in a solution of tetrahydrofuran and methanol. A warm water solution of 53 grams NaIO_4 was added dropwise. The reaction mixture was stirred for two hours at room temperature, then while the stirring was continued, ice water was added to obtain crystalline materials. The crude crystals were washed with water then stirred and suspended in 800 milliliters of water for 30 minutes. The crystals were filtered, washed with water and dried. The colorless crystal product weighed 27 grams (77 millimoles) which represents a 97% yield and had a melting point of 236°C to 238°C . The product, $11\beta,17\alpha$ -dihydroxy-1,4-diene-3-one- 17β -carboxylic acid, can be represented by the formula:



EXAMPLE 11

20 To an ice cooled mixture of $11\beta,17\alpha$ -dihydroxy-1,4-diene-3-one-17 β -carboxylic acid (5.2 grams; 15 millimoles) as prepared in Example 10 and KOH (6.7 grams; 12 moles) in 30 milliliters of dimethylsulfoxide was added 3.7 milliliters methyl iodide (60 millimoles) under nitrogen. The mixture was stirred for 5 hours at room temperature. The reaction mixture was diluted with ethyl acetate. The organic phase was separated and washed successively with water, $\text{Na}_2\text{S}_2\text{O}_3$ solution, NaHCO_3 solution and finally with water. The mixture was dried over MgSO_4 and the solvent was evaporated. The resulting crystalline material was recrystallized from CH_2Cl_2 hexane to afford colorless prisms. The product weighed 2.7 grams (7.2 millimoles) which represents an 83% yield and had a melting point of 241°C to 246°C. $\text{C}_{22}\text{H}_{30}\text{O}_5$ 374.47: Theoretical: H 8.07; C 70.56; Found: H 8.13; C 70.54. The product, methyl 11β -hydroxy- 17α -methoxy-3-oxo-androsta-1,4-diene-17 β -carboxylate, can be represented by the formula:



In a similar manner, substitution of an equivalent quantity of propyl iodide (5.8 milliliters; 60 millimoles) for the methyl iodide employed in the first part of this example and substantial repetition of the procedure 50 there detailed affords 1.9 gram propyl 11 β -hydroxy-17 α -propoxy-androsta-1,4-diene-3-one-17 β -carboxylate (4.4 moles; 29% yield). The final product, after crystallization from CH_2Cl_2 hexane, melts at 189°C to 190°C. $\text{C}_{25}\text{H}_{38}\text{O}_5$ 430.58; Theoretical: H 8.99; C 72.53; Found: H 9.04; C 72.26.

EXAMPLE 12

55 A mixture of 5.4 grams KOH (9 millimoles) and 4.5 grams methyl 11 β -hydroxy-17 α -methoxy-androsta-1,4-diene-3-one-17 β -carboxylate in 20 milliliters dimethylsulfoxide was stirred under nitrogen for five hours at 50°C. Water was added to the reaction mixture and the mixture was then acidified with 10% HCl. The

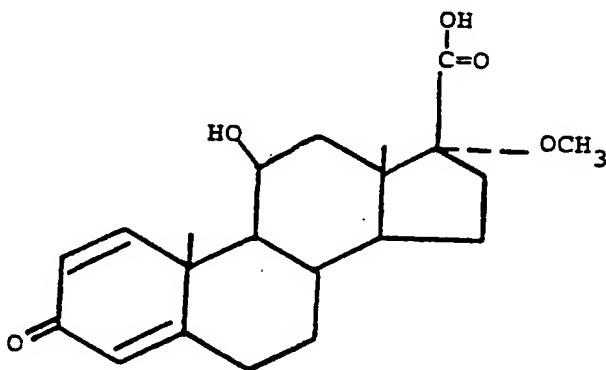
reaction mixture was stirred for 30 minutes. The ethylacetate extract was washed with water and the solvent was evaporated. The residual solid was neutralized with sodium bicarbonate solution and the mixture was washed with dichloromethane. The aqueous phase was acidified with 10% HCl and the deposited crystalline material was filtered under suction. The dried crude crystals were washed with water and dried. The crude product was subjected to silica gel chromatograph (MeOH/CH₂Cl₂) = 1/200-1/50. The product so obtained was recrystallized from methanol. The colorless prism product was 2.3 grams (6.4 millimoles) which represents yield of 53% and had a melting point of about 256 °C to 257 °C. C₂₁H₂₈O₅: 360.44: Theoretical: H 7.83; C 69.98; Found: H 8.02; C 70.01. The product, 11 β -hydroxy-17 α -methoxy-androsta-1,4-diene-3-one-17 β -carboxylic acid, can be represented by the formula:

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In a similar manner, the second product of Example 11, propyl 11 β -hydroxy-17 α -propoxy-androsta-1,4-

diene-3-one-17 β -carboxylate (1.6 gram; 3.7 millimoles) and 1.8 gram KOH (32 millimoles) in 20 milliliters

dimethylsulfoxide was heated at 50 °C under stirring in nitrogen for 20 hours. The crude acid was worked

up and chromatographically purified (MeOH/CH₂Cl₂ = 1/500-1/30). Recrystallization from ether afforded 0.62

grams 11 β -hydroxy-17 α -propoxy-androsta-1,4-diene-3-one-17 β -carboxylic acid representing a 43% yield

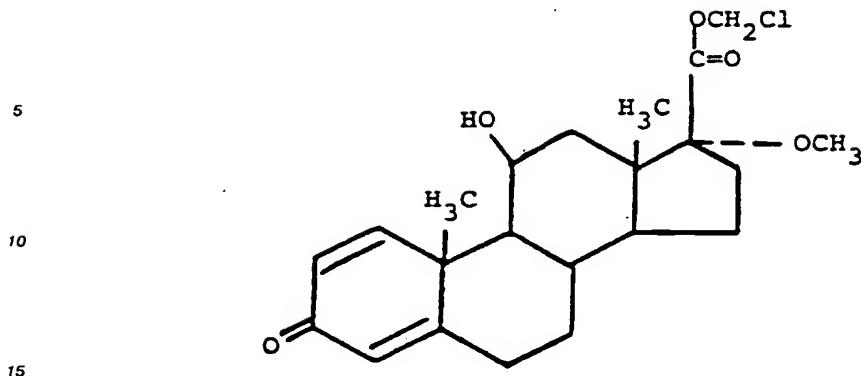
and had a melting point of 223 °C to 225 °C. C₂₃H₂O₅: 388.50: Theoretical: H 8.30; C 71.11; Found: H 8.74; C 71.05.

35 EXAMPLE 13

To 5 milliliters of 1 normal KOH/MeOH solution which was cooled with ice, was added 1.8 gram 11 β -hydroxy-17 α -methoxy-androsta-1,4-diene-3-one-17 β -carboxylic acid. The mixture was worked up to dryness under vacuum. The dried mixture was dissolved in 5 milliliters dimethylsulfoxide then 3.6 grams chloroiodomethane (20 millimoles) was added. The reaction mixture was stirred at room temperature for six hours. The ethylacetate extract was washed with water, sodium thiosulfate solution, sodium bicarbonate solution and finally with water. The solution was dried over MgSO₄ and the solvent was evaporated. After silica column chromatography (MeOH/CH₂Cl₂ = 250-1/100), the product was recrystallized from ethylacetate. The colorless prism product was 0.46 gram (1.1 millimoles) representing a yield of 22% and had a melting point of 217 °C to 218 °C. C₂₂H₂₉ClO₅: 408.92: Theoretical: H 7.15; C 64.62; Found: H 7.24; C 64.48. The product, chloromethyl 11 β -hydroxy-17 α -methoxy-androsta-1,4-diene-3-one-17 β -carboxylate, can be represented by the formula:

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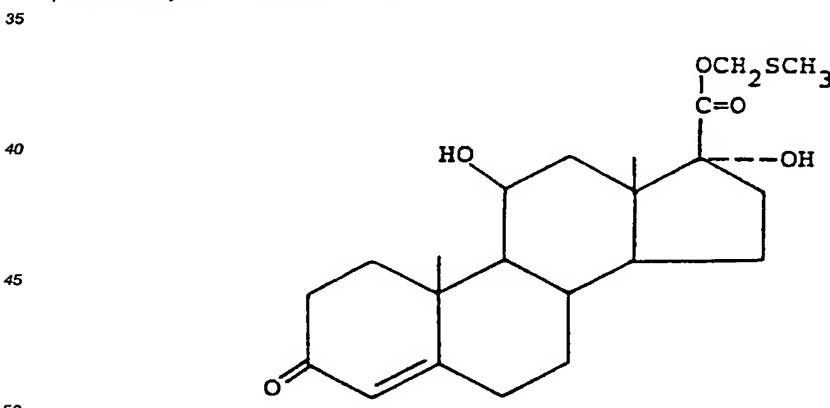
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In a similar manner, the second product of Example 12, 11β-hydroxy-17α-propoxy-androsta-1,4-diene-3-one-17β-carboxylic acid (0.55 gram; 1.4 millimole) was heated at the same manner to the first part of this example. Substantial repetition of the procedure there detailed afforded 34 milligrams chloromethyl 11β-20 hydroxy-17α-propoxy-androsta-1,4-diene-3-one-17β-carboxylate (0.08 millimoles) which represents a yield of 6% and a melting point of 184 °C to 187 °C. C₂₄H₃₃ClO₅:436.97: Theoretical: H 7.61; C 65.97; Found: H 7.74; C 65.65.

EXAMPLE 14

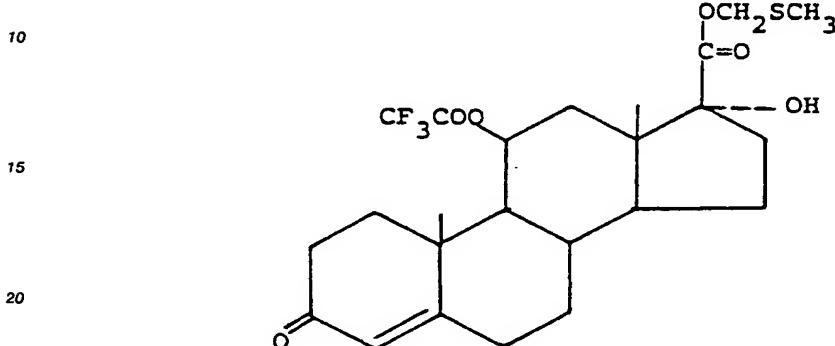
25 To a suspension of 11β,17α-dihydroxyandrost-4-en-3-one 17β-carboxylic acid (cortienic acid; 3.0 grams) in acetonitrile (30 milliliters) was added triethylamine (1.2 milliliters) followed by chloromethylmethylsulfide (CICH₂SCH₃). The resulting solution was refluxed overnight. After cooling at room temperature, the solvent was evaporated and the residue was triturated with tetrahydrofuran (30 milliliters). The precipitate 30 was filtered off and washed with additional tetrahydrofuran. The filtrates were combined and evaporated under reduced pressure to obtain 3.0 grams of product having the following: H nmr (CDCl₃): 1.06 (s, 3, 18CH₃); 1.47 (s, 3, 19CH₃); 2.30 (s, 3, SCH₃); 4.52 (m, 1, 11CH); 5.27 (s, 2, OCH₂SCH₃); 5.73 (s, 1, C=CH). The product, methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate, can be represented by the structural formula:



EXAMPLE 15

55 The methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate (0.817 gram) was stirred for 10 minutes in pyridine (10 ml) at -15 °C and trifluoroacetic anhydride (1.1 equivalent) was added dropwise. After stirring for 15 minutes at -15 °C, the cold bath was removed and the solution was allowed to slowly warm up to room temperature and poured into cold brine (100 milliliters). The resulting precipitate

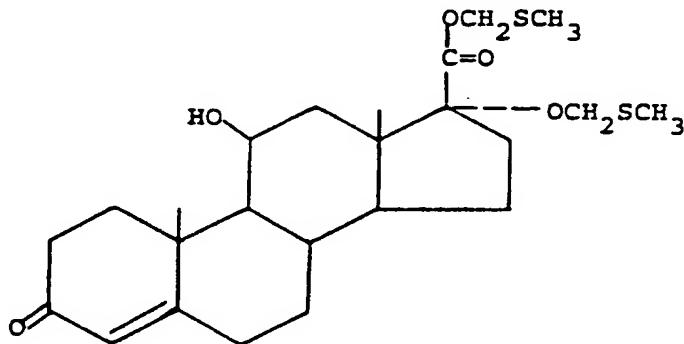
5 was stirred for 30 minutes and filtered off, washed with water and dried. The dried product was purified from 30 grams of silica gel and eluted with EtOAc/Hexane 20 to 60% and gave 0.75 gram of final product having the following elemental analysis: H nmr (CDCl₃): 0.92 (s, 3, 18CH₃); 1.29 (s, 3, 19CH₃); 2.24 (s, 3, SCH₃); 5.24 (ABq, $\Delta\nu$ =0.13 ppm; J_{AB}=12Hz, CH₂SCH₃O); 5.71 (m, 1, 11CH); 5.76 (s, 1, C=CH). IR (CDCl₃): 3400, 1780, 1730, 1670cm⁻¹. The product, methylthiomethyl 17 α -hydroxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:



EXAMPLE 17

5 The methylthiomethyl 17α -methylthiomethoxy- 11β -trifluoroacetoxyandrost-4-en-3-one- 17β -carboxylate (0.677 grams) was refluxed for four hours in wet methanol (10 milliliters) containing sodium bicarbonate (150 milligrams). The solution was then poured into cold stirring water (100 milliliters) and stirred another 30 minutes. The precipitate was filtered off, washed with water and dried.

10 The pure final product, from silica gel chromatography (17 g), eluting with EtOAc/Hexane 30:70 and crystallization from CH_2Cl_2 /Pentane, had a melting point of 195°C to 196°C. H nmr (CDCl_3): 1.01 (s, 3 18CH_3); 1.46 (s, 3, 19CH_3); 2.19 (s, 3, SCH_3); 2.41 (s, 3, SCH_3); 4.44 (m, 3, OCH_2S and 11CH); 5.21 (ABq, $\Delta\nu = 0.06$ ppm, $J_{AB} = 12\text{Hz}$, COOCH_2S); 5.71 (s, 1, $\text{C}=\text{CH}$). IR (KBr): 3400, 1730, 1655cm^{-1} . The product, methylthiomethyl 11β -hydroxy- 17α -methylthiomethoxyandrost-4-en-3-one- 17β -carboxylate, can be represented by the structural formula:

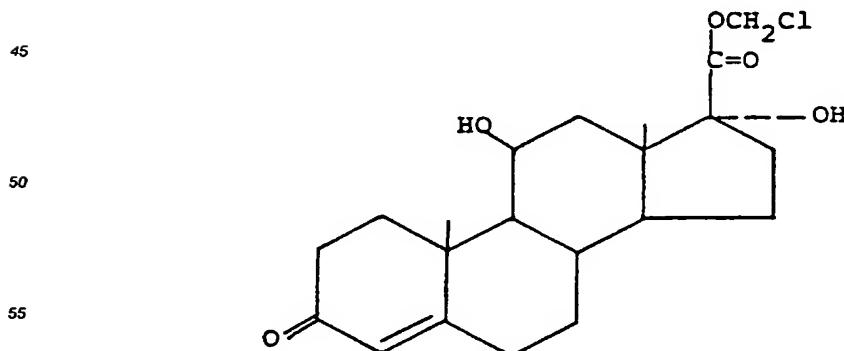
EXAMPLE 18

30 $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylic acid (cortienic acid; 3.48 grams) was suspended in methanol (10 milliliters) and a 1 normal solution of KOH in methanol (10 milliliters) was added dropwise. After concentration under vacuo and drying, the potassium salt was taken up into dimethylsulfoxide (10 milliliters) and treated with chloroiodomethane (1.5 milliliters). The reaction mixture was stirred at room temperature for five hours, partitioned between CH_2Cl_2 (100 milliliters) and water (100 milliliters). The organic layer was washed successively with 50 milliliters $\text{Na}_2\text{S}_2\text{O}_3$ (5% weight/volume), 50 milliliters of 5% NaHCO_3 and twice with 50 milliliters water. The product was dried over MgSO_4 , filtered and evaporated, giving a mixture containing the desired product plus a compound which was a dimer of the starting material.

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The pure compound had a melting point of 100°C to 192°C. The product, chloromethyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate, can be represented by the structural formula:



EXAMPLE 19

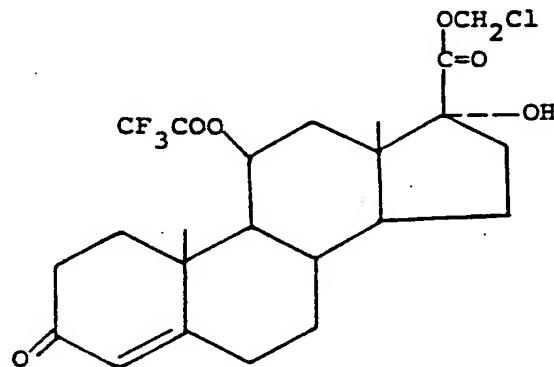
5 Chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate (3.48 grams) was reacted following the same procedure as in Example 15. Analysis: H nmr (CDCl₃): 0.91 (s, 3, 18CH₃); 1.30 (s, 3, 19CH₃); 5.73 (m, 4, C=CH plus 11CH plus COOCH₂Cl). The product, chloromethyl 17 α -hydroxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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EXAMPLE 20

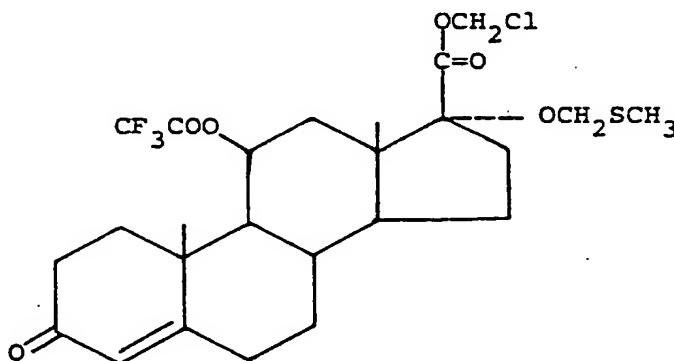
30 Chloromethyl 17 α -hydroxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate (3.48 grams) was reacted following the same procedure in Example 16. The final product had the following elemental analysis: H nmr (CDCl₃): 0.90 (s, 3, 18CH₃); 1.33 (s, 3, 19CH₃); 2.24 (s, 3, SCH₃); 4.43 (ABq, $\Delta\nu$ = 0.11ppm, J_{AB} = 11Hz, OCH₂S); 5.74 (m, 4, C=CH plus 11CH plus COOCH₂Cl). The product, chloromethyl 17 α -methylthiomethoxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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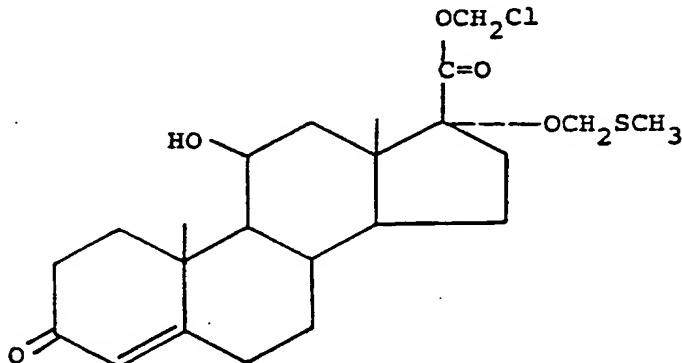
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EXAMPLE 21

55 The chloromethyl 17 α -methylthiomethoxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate, was reacted following the same procedure as Example 17. The final product had the following elemental analysis: H nmr (CDCl₃): 1.00 (s, 3, 18CH₃); 1.30 (s, 3, 19CH₃); 2.18 (s, 3 SCH₃); 4.41 (ABq, $\Delta\nu$ = 0.06ppm; J_{AB} = 6Hz; OCH₂S); 4.44 (m, 1, 11CH); 5.67 (s, 1, C=CH); 5.77 (ABq, $\Delta\nu$ = 0.06ppm, J_{AB} = 6Hz; COOCH₂Cl).

The product, chloromethyl 11 β -hydroxy-17 α -methylthiomethoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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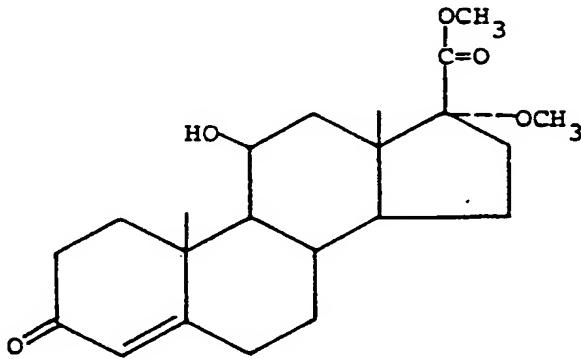
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EXAMPLE 22

Powdered potassium hydroxide (2.14 grams) was stirred for five minutes into dimethylsulfoxide (10 milliliters). 11 β -17 α -Dihydroxyandrost-4-en-3-one-17 β -carboxylic acid (cortienic acid; 1.7 grams; 4.88 millimoles) was immediately added followed by methyl iodide (1.22 milliliters; 19.5 millimoles). After stirring for one hour and 15 minutes at 25 °C, the mixture was diluted with ethylacetate (100 milliliters) and washed successively with 10 milliliters water, 10 milliliters Na₂S₂O₃ (5% weight/volume), 10 milliliters NaHCO₃ (5% weight/volume) and three more times with 10 milliliters water. The organic solution was then dried over MgSO₄ and evaporated under partial pressure. The white, crystalline, crude product weighed 1.73 grams (94% theoretical) and had a melting point of 195 °C to 201 °C. Crystallization from CH₂Cl₂/Pentane raised the melting point to 215 °C to 217 °C, then 217 °C to 218.5 °C. Elemental analysis: required C₂₀H₃₀O₄; found C₂₀H₃₀O₄. The product, methyl 11 β -hydroxy-17 α -methoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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EXAMPLE 23

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The methyl 11 β -hydroxy-17 α -methoxyandrost-4-en-3-one-17 β -carboxylate, (3.76 grams; 10 millimoles), was stirred overnight (16 hours) at 50 °C, under nitrogen, in a mixture compound of powdered potassium hydroxide (4.50 grams) and dimethylsulfoxide (15 millilitres). The reaction mixture is then diluted into water

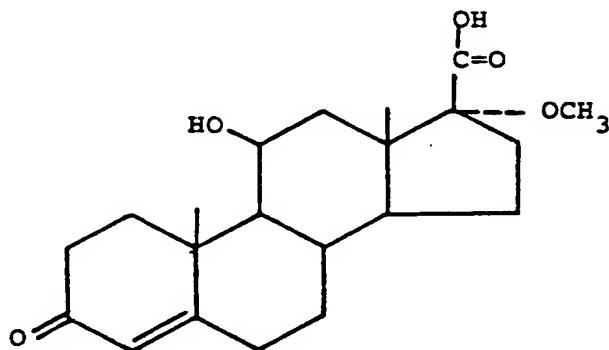
(200 milliliters), acidified with HCl, stirred 30 minutes and extracted with several portions of ethyl acetate. The organic layer was then washed with water (30 milliliters), evaporated and taken up into 150 milliliters of NaHCO₃ solution (5% weight/volume). This aqueous solution was washed with 30 ml of methylene chloride, acidified with diluted HCl, filtered, and the residue is dried in *vacuo* at 40 °C overnight. The yellow, 5 pseudocrystalline, crude product weighed 3.05 g (84% theor.). Elemental analysis: ¹H nmr (DMSO-d₆): 0.92 (s, 3, 18CH₃); 1.38 (s, 3, 19CH₃); 3.04 (s, 3, OCH₃); 5.50 (s, 1, C=CH); 8.28 (s, <1, COOH). Purification from Silica gel (CCl₄), eluting with EtOAc/Hexane 50:50 and crystallization from acetone gave a compound melting at 214 °C to 216 °C, with satisfactory elemental analysis. The product, 11 β -hydroxy-17 α -methoxyandrost-4-en-3-one-17 β -carboxylic acid, can be represented by the structural formula:

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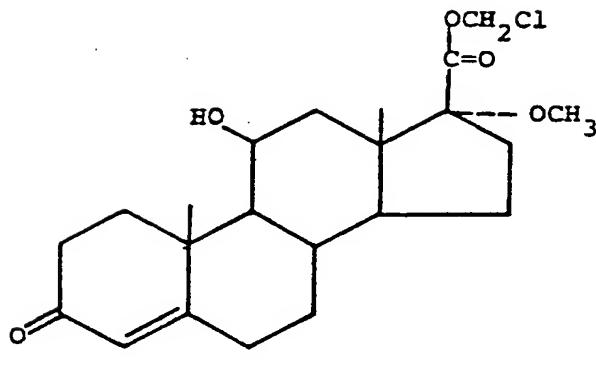
EXAMPLE 24

30 The 11 β -hydroxy-17 α -methoxyandrost-4-en-3-one-17 β -carboxylic acid, (1 millimole) was suspended in methanol (5 millilitres) and a 1 normal solution of KOH in methanol (1 milliliter) was added dropwise at 0 °C (ice bath). The solution was evaporated under *vacuo*, dried thoroughly, and the resulting potassium salt was mixed with dimethylsulfoxide (10 milliliters) and chloriodomethane (4 millimoles). After stirring for 7 hours at room temperature (24 °C), the mixture (containing a precipitate of potassium iodide) was diluted with ethylacetate (100 milliliters) and washed successively with 10 milliliters water, 10 milliliters Na₂S₂O₃ (5% weight/volume), 10 milliliters NaHCO₃ and 3 times with water (10 milliliters) and dried over MgSO₄ and evaporated under partial pressure. Purification by column chromatography from 12 grams of Silica gel (100-200 mesh type 60A) eluting with EtOAc/CHCl₃ 20:80 and crystallization from ethylacetate/ether gave a product that melts at 195 ° to 196 °C. ¹H nmr (CDCl₃): 0.95 (s, 3, 18CH₃); 1.43 (s, 3, 19CH₃); 3.12 (s, 3, OCH₃); 5.60 (s, 1, C=CH); 5.75 (s, 2, COOCH₂Cl). IR (KBr): 3400, 1755, 1655, 1205, 2110 (ether) cm⁻¹. 35 Elemental analysis: Required: C64.30; H7.60; C18.63; Found: C64.16; H7.63; C18.63. The product, chloromethyl 11 β -hydroxy-17 α -methoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the formula:

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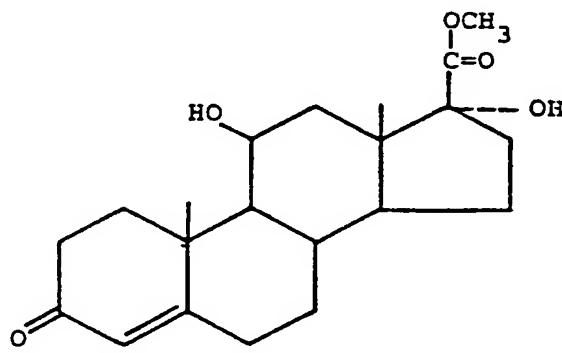
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EXAMPLE 25

20 $11\beta,17\alpha$ -Dihydroxyandrost-4-en-3-one- 17β -carboxylic acid (cortienic acid; 3.434 grams; 10 millimoles) was dissolved in methylalcohol, then a 1 normal solution of KOH in MeOH (10 milliliters) was added dropwise in the cold. The solution was evaporated under vacuo and the residue was dried thoroughly and taken up into dimethylsulfoxide (20 milliliters) and methyl iodide (2.5 milliliters; 40 millimoles). After stirring overnight at room temperature, the mixture was diluted with ethylacetate (15 milliliters) and washed successively with 50 milliliters NaHCO_3 (3% weight/volume), 50 milliliters $\text{Na}_2\text{S}_2\text{O}_3$ (5% weight/volume) and three times with 50 milliliters water, dried over MgSO_4 , and evaporated. The product crystallized from ethylacetate, and 3 crops gave 3.31 g (92%) of white crystals melting at 206 °C to 207 °C (litt. 207 °C to 208 °C). ^1H nmr (CDCl_3): 0.98 (s, 3, 18CH_3); 1.45 (s, 3, 19CH_3); 3.75 (s, 3, COOCH_3); 5.67 (s, 1, $\text{C}=\text{CH}$). The product, methyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate, can be represented by the structural formula:

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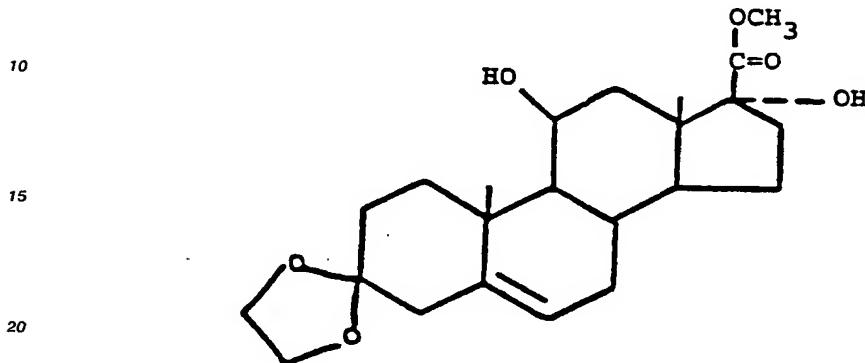
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EXAMPLE 26

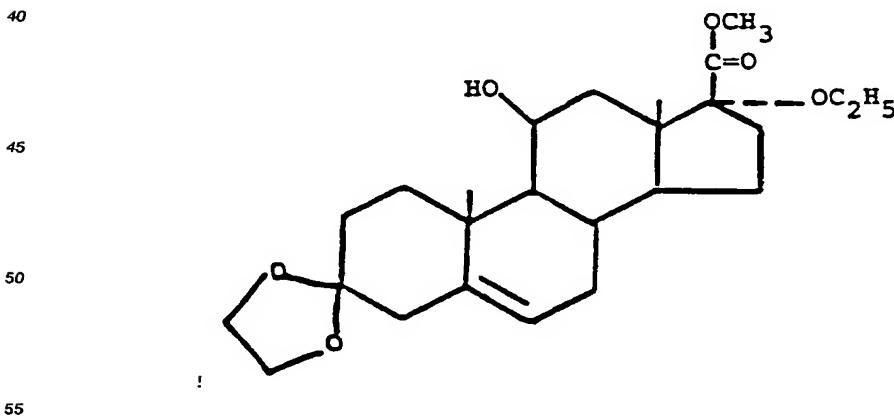
50 The methyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate, (10.32 grams; 22.5 millimoles), was taken up into ethylene glycol (170 milliliters) and p-toluenesulfonic acid (anhydrous, crystallized from benzene; 85 milligrams) was added. The solvent was slowly distilled off at 0.3-1 mm Hg for 2 hours. The distillation lead was 60 °C to 70 °C and the mixture turned red after about 30 minutes. The suspension was neutralized with NaHCO_3 (the mixture turned colorless), poured into cold water (200 milliliters) and stirred for at least 30 minutes. The white precipitate was isolated by filtration, washed with water and dried in the freeze dryer. Thin layer chromatography showed a small amount of starting material and a few percent of a product identified as the $\Delta^{9,11}$ 3,3' cyclic ketal. Triturating the product with a few milliliters of ether yielded

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white crystals having a melting point of 204°C to 205°C with satisfactory elemental analysis. Theoretical: C67.96; H8.43; Found: C67.71; H8.47. ^1H nmr (CDCl_3): 0.93 (s, 3, 18CH_3); 1.27 (s, 3, 19CH_3); 3.70 (s, 3, COOCH_3); 3.90 (s, 4, $\text{OCH}_2\text{CH}_2\text{O}$); 5.12 (s, 3, 19CH_3); 3.70 (s, 3, COOCH_3); 3.90 (s, 4, $\text{OCH}_2\text{CH}_2\text{O}$); 5.12 (s, 1, $\text{C}=\text{CH}$). The product, methyl 3-(1',3'-dioxacyclopent-2'-yl)-11 β ,17 α -dihydroxyandrost-5-en-3-one-17 β -carboxylate, can be represented by the structural formula:

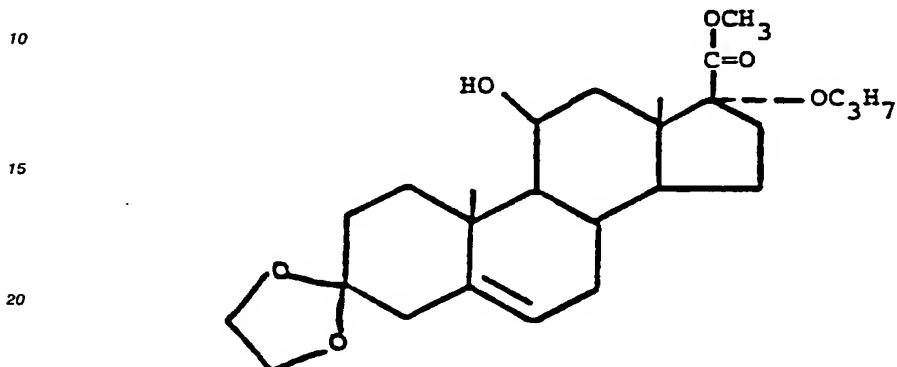
25 EXAMPLE 27

Powdered KOH (1.2 grams) was stirred for five minutes into dimethylsulfoxide (15 milliliters), then the methyl 3-(1',3'-dioxacyclopent-2'-yl)-11 β ,17 α -dihydroxyandrost-5-en-3-one-17 β -carboxylate (2.15 grams; 5.3 millimoles) was added, immediately followed by iodoethane (1.7 milliliters, 21.2 millimoles) and the mixture was stirred at 25°C for 23 hours. The reaction was then diluted with ethylacetate (150 milliliters) and washed successively with 50 milliliters $\text{Na}_2\text{S}_2\text{O}_3$ (5% weight/volume) and three times with 50 milliliters water, dried over MgSO_4 and evaporated to give 1.92 grams of crude product (83% theoretical). Some product was extracted with the aqueous phase and was identified as cortienic acid-3,3' cyclic ketal. Purification from 45 grams of silica gel and eluting with benzene/EtOAc 80:20 yielded 1.1 g of a white compound. IR (KBr): 3500, 1725, 1215, 1110, 1085 cm^{-1} . ^1H nmr 0.90 (s, 3, 18CH_3); 1.10 (t, 3, $J=7\text{Hz}$, OCH_2CH_3); 1.28 (s, 3, 19CH_3); 3.32 (m, 2, OCH_2CH_3); 3.70 (s, 3, COOCH_3); 3.95 (s, 4, $\text{OCH}_2\text{CH}_2\text{O}$); 5.15 (s, 1, $\text{C}=\text{CH}$). The product, methyl 3-(1',3'-dioxacyclopent-2'-yl)-17 α -ethoxy-11 β -hydroxyandrost-5-en-3-one-17 β -carboxylate, can be represented by the structural formula:

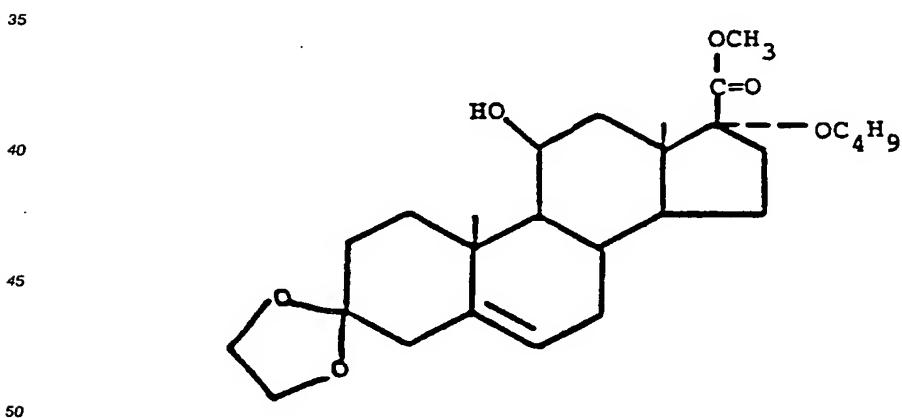


EXAMPLE 28

5 The methyl 3-(1',3'-dioxacyclopent-2'-yl)-11 β ,17 α -dihydroxyandrost-5-en-3-one-17 β -carboxylate and iodopropane were reacted following the same procedure in Example 27. The H nmr spectrum was identical (without the triplet at 1.10 ppm). The product, methyl 3-(1',3'-dioxacyclopent-2'-yl)-11 β -hydroxy-17 α -propoxyandrost-5-en-3-one-17 β -carboxylate, can be represented by the following structural formula:

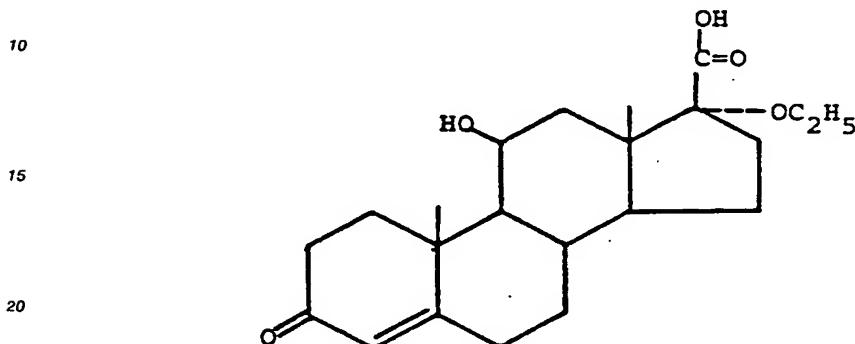
EXAMPLE 29

30 The methyl 3-(1',3'-dioxacyclopent-2'-yl)-11 β ,17 α -dihydroxyandrost-5-en-3-one-17 β -carboxylate and bromobutane were reacted following the same procedure in Example 25 except that a ratio of 4:1 of bromobutane to the 17 α -hydroxy compound was used and the reaction was allowed to proceed for three days. The crude product was a mixture of the methyl and butyl ester. The butyl ester, methyl 3-(1',3'-dioxacyclopent-2'-yl)-17 α -butoxy-11 β -dihydroxyandrost-5-en-3-one-17 β -carboxylate, can be represented by the structural formula:

EXAMPLE 30

55 The chloromethyl 11 β -hydroxy-17 α -methylthiomethoxyandrost-4-en-3-one-17 β -carboxylate (1.1 grams; 2.5 millimoles) was stirred for 17 hours under nitrogen at 60 °C in dimethylsulfoxide (5 milliliters) containing powdered KOH (0.5 gram). The reaction was then taken up into water (150 milliliters), acidified slowly with dilute HCl to pH 1-2, stirred for 15 minutes and extracted four times with EtOAc (80 milliliters), dried over

MgSO₄ and evaporated. The crude product was dissolved into NaHCO₃ (13% weight/volume), washed with EtOAc and acidified. Drying gave 669 mg (64%) of product. IR (KBr): 3500, 1715, 1670, 1085 cm⁻¹. H nmr (DMSO₄): 0.92 (s, 3, 18CH₃); 1.05 (t, 3, J = 7Hz, OCH₂CH₃); 1.37 (s, 3, 19CH₃); 3.28 (m, 2, OCH₂CH₃); 5.55 (s, 1, C = CH). Purification from CCl₄ silica gel and crystallization from acetone gave a compound melting at 236 °C to 240 °C with satisfactory elemental analysis. The product, 17 α -ethoxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acid, can be represented by the structural formula:



EXAMPLE 31

11 β -Hydroxy-17 α -propoxyandrost-4-en-3-one-17 β -carboxylic acid and 17 α -butoxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acid were prepared following a similar procedure to Example 30 and gave satisfactory elemental analysis.

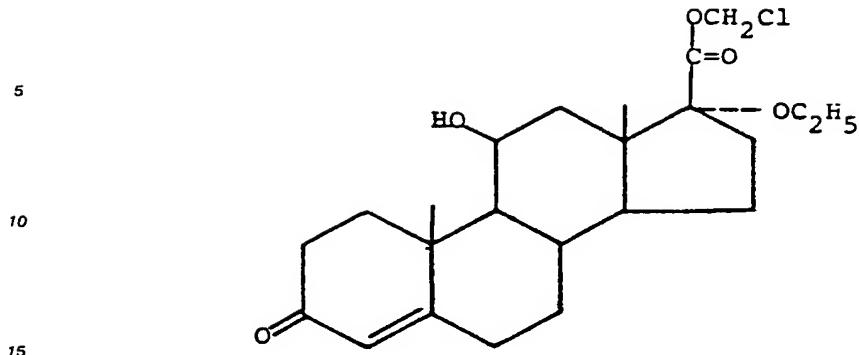
EXAMPLE 32

The 17 α -ethoxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acid (1.58 millimoles) was converted to the potassium salt following the same procedure as Example 24. The potassium salt was stirred at room temperature for eight hours in dimethylsulfoxide (10 milliliters) containing chloroiodomethane (1.25 milliliters). After the work-up used in Example 24, 0.594 grams of crude product was obtained which was chromatographed on 15 grams silica gel, eluted with Hexane/EtOAc 80:20 then 70:30. Crystallization from CH₂Cl₂/Pentane gave white crystals melting at 203 °C to 205 °C. IR (KBr): 3400, 1750, 1650, 1205, 1110, 1060 cm⁻¹. H nmr (CDCl₃): 0.95 (s, 3, 18CH₃); 1.13 (t, 3, J = 7Hz, OCH₂CH₃); 1.43 (s, 3, 19CH₃); 3.38 (m, 2, OCH₂CH₃); 5.65 (s, 1, C = CH); 5.77 (s, 2, COOCH₂Cl). Elemental analysis: Required: C65.08; H7.83; C18.34; Found: C64.86; H7.84; C18.32. The product, chloromethyl 17 α -ethoxy 11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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EXAMPLE 33

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Chloromethyl 11β-hydroxy-17α-propoxyandrost-4-en-3-one-17β-carboxylate was prepared following a similar procedure as Example 32 and had a melting point of 194°C to 195°C. IR (KBr): 3400, 1750, 1650, 1205, 1110, cm^{-1} ; H nmr (CDCl_3): 0.88 (t, 3, $J=7\text{Hz}$, $\text{OCH}_2\text{CH}_2\text{CH}_3$); 0.98 (s, 3, 18CH_3); 1.42 (s, 3, 19CH_3); 3.18 (m, 2, $\text{OCH}_2\text{CH}_2\text{CH}_3$); 5.65 (s, 1, $\text{C}=\text{CH}$); 5.77 (s, 2, COOCH_2Cl). Elemental analysis: Theoretical: C65.65; H8.04; C18.08; Found: C65.78; H8.09; C18.14.

EXAMPLE 34

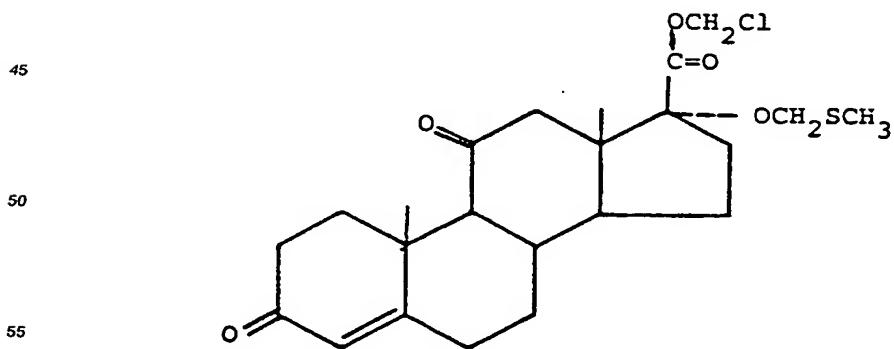
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Chloromethyl 17α-butoxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate was prepared following a similar procedure as Example 32 and had a melting point of 100°C to 151°C. IR (KBr) 3400, 1750, 1645, 1200, 1110 H nmr (CDCl_3): 0.98 (s, 3, 18CH_3); 1.45 (s, 3, 19CH_3); 3.28 (m, 2, $\text{OCH}_2\text{CH}_2\text{CH}_3$); 5.65 (s, 1, $\text{C}=\text{CH}$); 5.77 (s, 2, COOCH_2Cl).

EXAMPLE 35

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The chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate was treated under the same conditions as Example 20. IR (KBr): 1755, 1705, 1660 cm^{-1} . H nmr (CDCl_3): 0.67 (s, 3, 18CH_3); 1.40 (s, 3, 19CH_3); 2.09 and 2.23 (2s, 12CH_2), 2.19 (s, 3, SCH_3); 4.45 (ABq, $\Delta\nu=0.06$ ppm, $J_{\text{AB}}=12\text{Hz}$, OCH_2S); 5.71 (s, 1, $\text{C}=\text{CH}$); 5.87 (s, 2, OCH_2Cl). The product, chloromethyl-17 α -methylthio-methyloxyandrost-4-en-3,11-dione-17 β -carboxylate, can be represented by the structural formula:



EXAMPLE 36

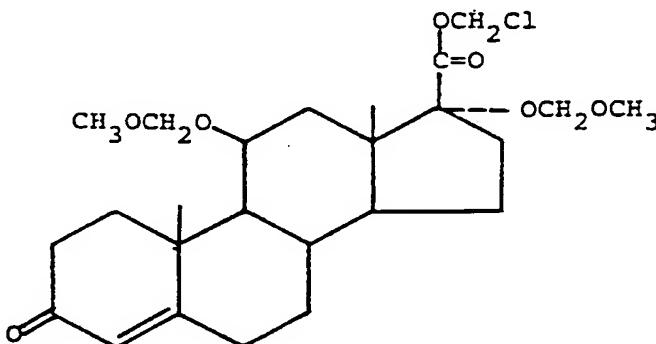
The chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate (80 milligrams), was taken up into dry CH_2Cl_2 (5 milliliters) and methylal (2 milliliters). A mixture of P_2O_5 /silica gel 1:2 (100 milligrams) was added, while stirring. After stirring 7 hours at room temperature, the mixture was filtered, the silica gel was washed with CH_2Cl_2 . The organic extracts were washed with concentrated NaHCO_3 solution and water. H nmr (CDCl_3): 0.83 (s, 3, 18CH_3); 1.41 (s, 3, 19CH_3); 3.40 (s, 3, OCH_3); 4.6 (2ABq, 11 β and 17 α - OCH_2O); 5.66 (s, 1, $\text{C}=\text{CH}$); 5.76 (ABq, $\Delta\nu = 0.27$ ppm; $J_{\text{AB}} = 6\text{Hz}$; OCH_2Cl). The product, chloromethyl 11 β ,17 α -di(methoxymethoxy)androst-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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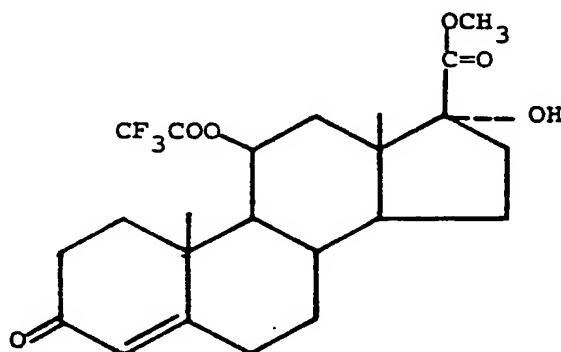
EXAMPLE 37

30 The chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate was treated at -78°C according to the procedure of Example 15 to obtain 2.44 grams of methyl-17 α -hydroxy-11 β -trifluorooacetoxyandrost-4-en-3-one-17 β -carboxylate and 350 milligrams of the disubstituted side product, methyl 11 β ,17 α -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate. The product is easily separated by chromatography on 60 grams silica gel, eluting with EtOAc/Hexane 50:50. H nmr (CDCl_3): 0.82 (s, 3, 18CH_3); 1.27 (s, 3, 19CH_3); 3.70 (s, 3, COOCH_3); 5.69 (M, 2, $\text{C}=\text{CH}$ and 11 CH). IR (KBr): 1780; 1730; 1660 cm^{-1} . Elemental analysis: Required: C 60.25, H 6.38; Found: C 60.43, H 6.49. The product can be represented by the structural formula:

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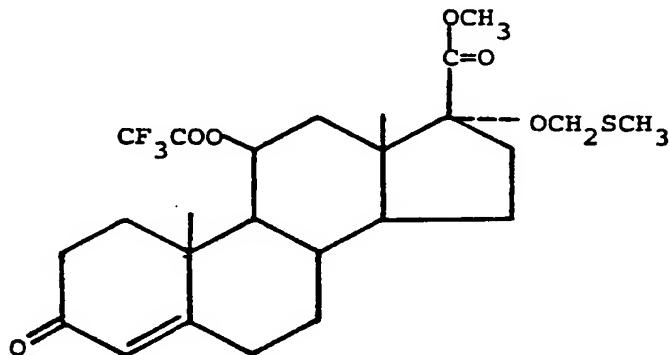
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55 The side product can easily hydrolyzed to the product, methyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate, by refluxing in $\text{MeOH}/\text{H}_2\text{O}/\text{NaHCO}_3$ following the procedure of Example 17.

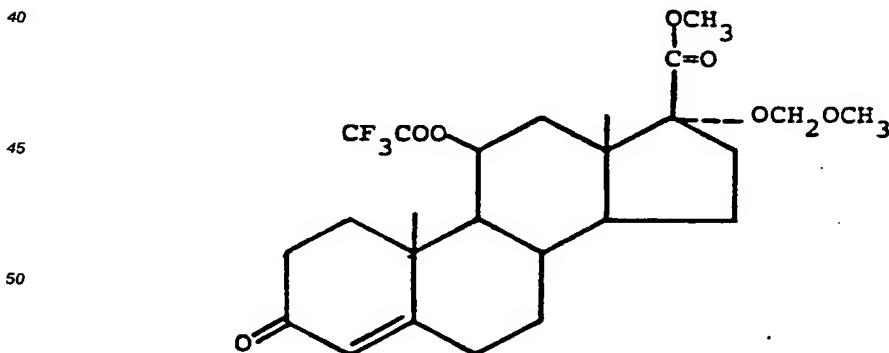
EXAMPLE 38

The methyl 17 α -hydroxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate (3.0 grams) was treated following the procedure of Example 16 to obtain 3.1 grams of product. H nmr (CDCl₃): 0.80 (s, 3, 18CH₃); 1.26 (s, 3, 19CH₃); 2.14 (s, 3, SCH₃); 3.70 (s, 3, COOCH₃); 4.37 (ABq, $\Delta\nu$ = 0.1 ppm; J_{AB} = 10Hz, OCH₂S); 5.70 (m, 2, 11CH and C = CH). The product, methyl 17 α -methylthiomethoxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:



EXAMPLE 39

The methyl 17 α -hydroxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate (5.43 grams) in dry CH₂Cl₂ (50 milliliters) and methylal (50 milliliters) was treated with a mixture of P₂O₅ (6 grams) and silica gel (12 grams) at 0°C. After stirring for seven hours at 0°C, the mixture was filtered and the residue washed with CH₂Cl₂. The organic phase was then washed with saturated NaHCO₃ solution and water, dried over MgSO₄ and concentrated in vacuo. Column chromatography on 200 g silica gel, eluting with CH₂Cl₂/EtOAc 90:10 yielded 4.0 g of product and 0.7 g of a compound identified as the 6 methylene derivative (by nmr and uv). H nmr (CDCl₃): 0.80 (s, 3, 18CH₃); 1.26 (s, 3, 19CH₃); 3.31 (s, 3, OCH₃); 3.68 (s, 3, COOCH₃); 4.60 (ABq, $\Delta\nu$ = 0.18 ppm, J_{AB} = 7Hz; OCH₂O); 5.70 (m, 2, 11CH and C = CH). The product, methyl 17 α -methoxymethoxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:



EXAMPLE 40

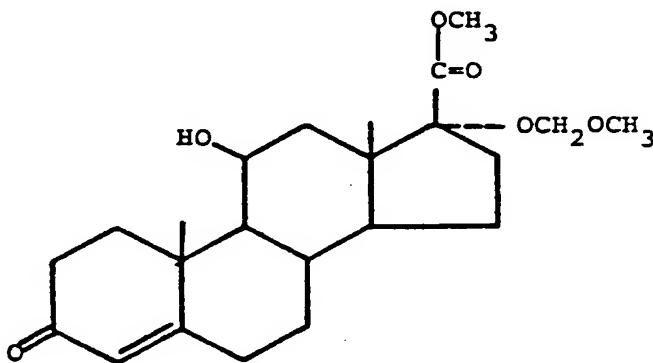
5 The methyl 17 α -methoxymethoxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate was treated following the procedure of Example 17. H nmr (CDCl₃): 0.96 (s, 3, 18CH₃); 1.44 (s, 3, 19CH₃; 3.31 (s, 3, OCH₃); 3.70 (s, 3, COOCH₃); 4.46 (m, 1, 11CH); 4.61 (ABq, $\Delta\nu$ = 0.16 ppm, J_{AB} = 7Hz, OCH₂O); 5.68 (s, 1, C=CH). The product, methyl 11 β -hydroxy-17 α -methoxymethoxyandrost-4-en-3-one-17 β -carboxylate, can be represented by the structural formula:

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EXAMPLE 41

30 The methyl 17 α -methylthiomethoxy-11 β -trifluoroacetoxyandrost-4-en-3-one-17 β -carboxylate was treated following the procedure of Example 17. The product was methyl 11 β -hydroxy-17 α -methylthiomethoxyandrost-4-en-3-one-17 β -carboxylate.

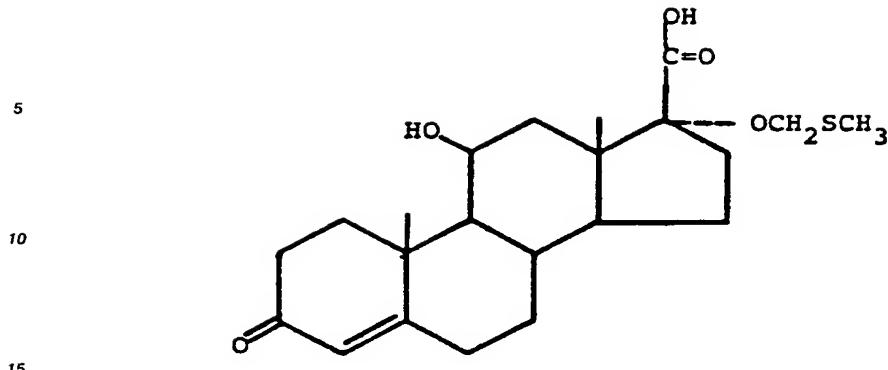
EXAMPLE 42

35 The methyl 11 β -hydroxy-17 α -methylthiomethoxyandrost-4-en-3-one-17 β -carboxylate, (882 milligrams) was treated at room temperature with a 1 normal solution of potassium tertiobutoxide in dimethylsulfoxide (5 milliliters). After 45 minutes under nitrogen, the mixture was poured into water (50 milliliters) and extracted with CH₂Cl₂. The aqueous layer was then combined with EtOAc (50 milliliters) and acidified slowly with 1 normal HCl while stirring. After extracting several times with EtOAc, the organic layers were dried over 40 MgSO₄ and concentrated *in vacuo*. H nmr (DMSO_d₆) 0.94 (s, 3, 18CH₃); 2.10 (s, 3, SCH₃); 4.26 (m, 1, 11CH); 4.37 (ABq, $\Delta\nu$ = 0.13 ppm, J_{AB} = 11Hz, CH₂SCH₃); 5.56 (s, 1, C=CH). The product, 11 β -hydroxy-17 α -methylthiomethoxyandrost-4-en-3-one-17 β -carboxylic acid, can be represented by the structural formula:

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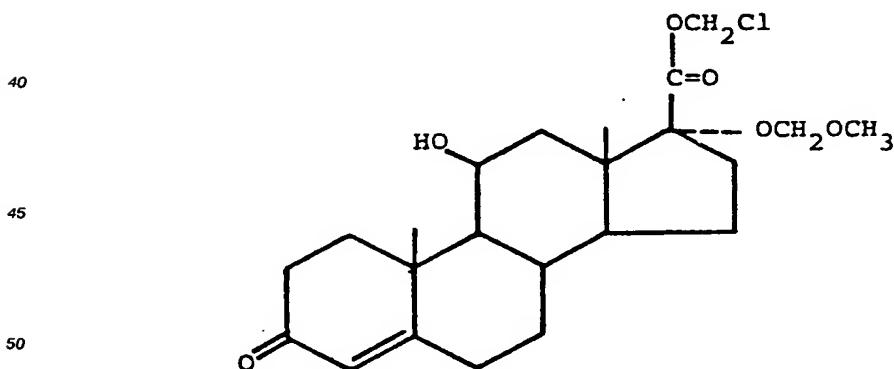
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EXAMPLE 43

20 The methyl 11β-hydroxy-17α-methoxymethoxyandrost-4-en-3-one-17β-carboxylate was reacted following the procedure of Example 42. H nmr ($\text{DMSO-}d_6$): 0.94 (s, 3, 18CH_3); 1.39 (s, 3, 19CH_3); 3.24 (s, 3, OCH_3); 4.56 (ABq, $\Delta\nu = 0.08$ ppm, $J_{\text{AB}} = 7\text{Hz}$, OCH_2O); 4.26 (m, 1, $11\bar{\text{C}}\text{H}$); 5.56 (s, 1, $\text{C}=\bar{\text{C}}\text{H}$). m.p. 207-209°C. The product is 11β-hydroxy-17α-methoxymethoxyandrost-4-en-3-one-17β-carboxylic acid.

EXAMPLE 44

25 The 11β-hydroxy-17α-methoxymethoxyandrost-4-en-3-one-17β-carboxylic acid was introduced into a mixture composed of water (20 milliliters, CH_2Cl_2 (10 milliliters) and NaHCO_3 (1.60 grams), then tetrabutylammonium hydrogen sulfate (0.105 grams) was added. After stirring for five minutes, a mixture of 30 chloromethyl chlorosulfate (1.1 equivalent) in CH_2Cl_2 (10 milliliters) was slowly added over a period of 30 minutes. The mixture was then stirred an additional 30 minutes. The organic phase was separated, dried over Na_2SO_4 and concentrated in *vacuo*, to give the product in yield. H nmr (CDCl_3): 1.02 (s, 3, 18CH_3); 3.33 (s, 3, OCH_3); 4.43 (m, 1, $11\bar{\text{C}}\text{H}$); 4.62 (ABq, $\Delta\nu = 0.17$ ppm, $J_{\text{AB}} = 7\text{Hz}$, OCH_2O); 5.67 (s, 1, $\text{C}=\bar{\text{C}}\text{H}$); 5.74 (ABq, $\Delta\nu = 0.14$ ppm, $J_{\text{AB}} = 6\text{Hz}$, OCH_2Cl). The product, chloromethyl 11β-hydroxy-17α-methoxymethoxyandrost-4-en-3-one-17β-carboxylate, can be represented by the structural formula:



55 From the foregoing description, one of ordinary skill in the art can readily ascertain the essential characteristics of the present invention and, without departing from the spirit and scope thereof, can make various changes and/or modifications of the invention to adapt it to various usages and conditions. As such, these changes and/or modifications are properly, equitably and intended to be within the full range of equivalence of the following claims.

Claims

1. A compound selected from the group consisting of:
 (a) a compound of the formula

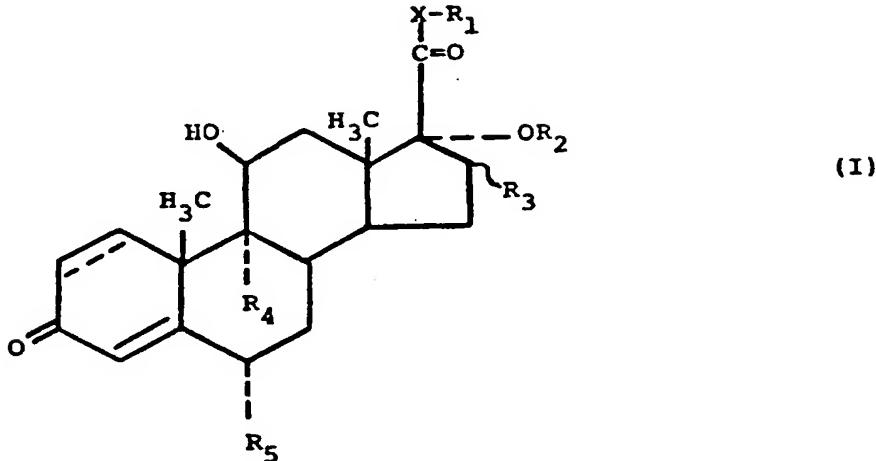
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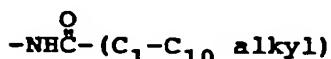
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wherein:

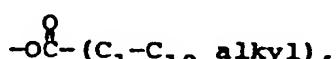
30 R_1 is C_1-C_{10} alkyl; C_2-C_{10} (monohydroxy or polyhydroxy) alkyl; C_1-C_{10} (monohalo or polyhalo)-alkyl; or $-CH_2COOR_6$ wherein R_6 is unsubstituted or substituted C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl or C_2-C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,

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and

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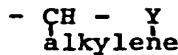
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or R_6 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxy carbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)-carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R_1 is $-CH_2CONR_7R_8$ wherein R_7 and R_8 , which can be the same or different, are each hydrogen, lower alkyl, C_3-C_8 cycloalkyl, phenyl or benzyl, or R_7 and R_8 are combined such that $-NR_7R_8$ represents the residue of a saturated monocyclic secondary amine; or R_1 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to R_6 ; or R_1 is

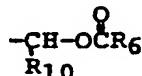
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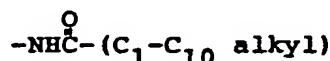
wherein Y is $-S-$, $-SO-$, $-SO_2-$ or $-O-$ and R_9 is hydrogen, lower alkyl or phenyl, or R_9 and the lower alkyl group adjacent to Y are combined so that R_1 is a cyclic system of the type



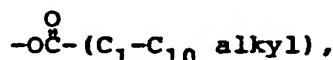
5 wherein Y is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms; or R₁ is



15 wherein R₆ is defined as hereinabove and R₁₀ is hydrogen, lower alkyl, phenyl or halophenyl; R₂ is unsubstituted or substituted C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl or C₂-C₁₀ alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,



and



30 or R₂ is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxy carbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)-carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl;

35 R₃ is hydrogen, α -hydroxy, β -hydroxy, α -methyl, β -methyl, =CH₂, or α - or β -OR₂ wherein R₂ is identical to R₂ as defined hereinabove;

R₄ is hydrogen, fluoro or chloro;

R₅ is hydrogen, fluoro, chloro or methyl;

X is -O- or -S-;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated;

(b) a quaternary ammonium salt of a compound of formula (I) wherein at least one of R₁ and R₂ is a halo-substituted alkyl group;

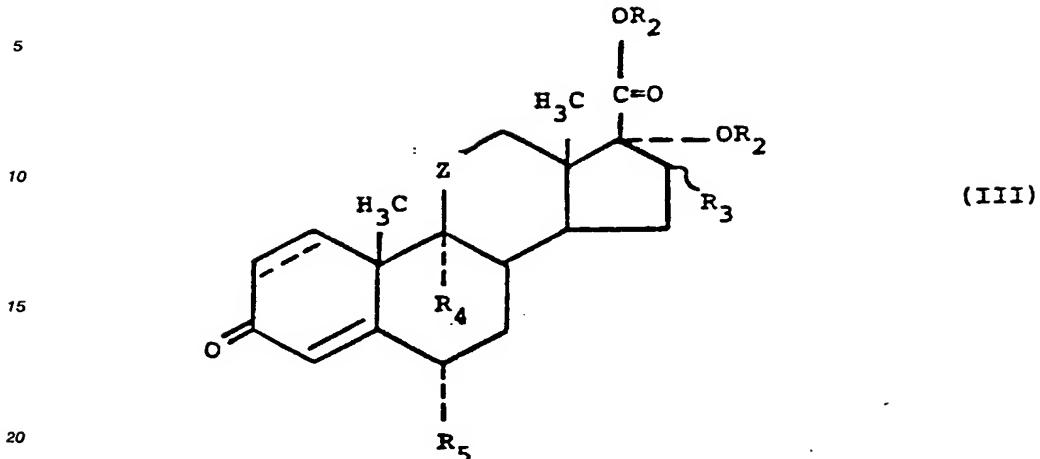
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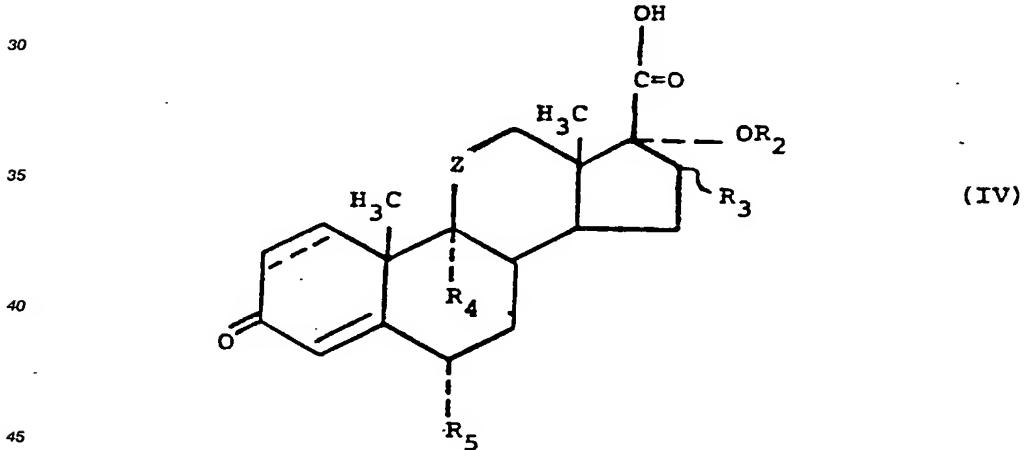
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(c) a compound of the formula



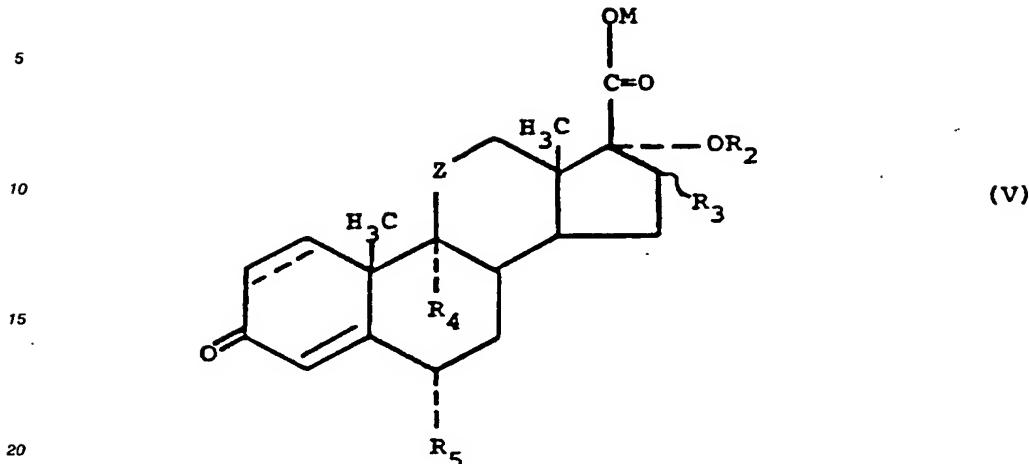
25 wherein R_2 , R_4 , R_5 , and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β -hydroxymethylene and R_3 is hydrogen, α -methyl, β -methyl, $=CH_2$ or α - or β - OR_2 wherein R_2 is identical to R_2 above;

(d) a compound of the formula



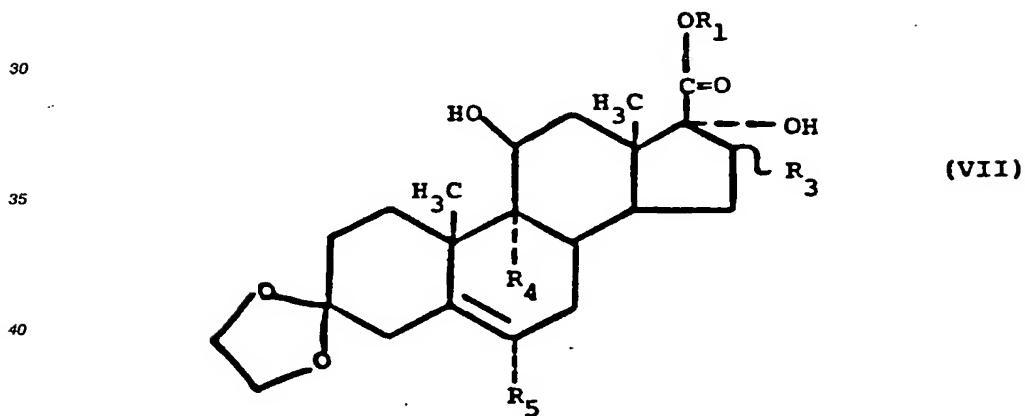
50 wherein R_2 , R_4 , R_5 , and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β -hydroxymethylene and R_3 is hydrogen, α -methyl, β -methyl, $=CH_2$ or α - or β - OR_2 wherein R_2 is identical to R_2 above;

(e) a compound of the formula



wherein M is alkali metal, thallium, alkaline earth metal/2 or NH_4 and R_2 , R_3 , R_4 , R_5 , Z and the dotted line in ring A are as defined in (a) and (d) above;

25 f) a compound of the formula

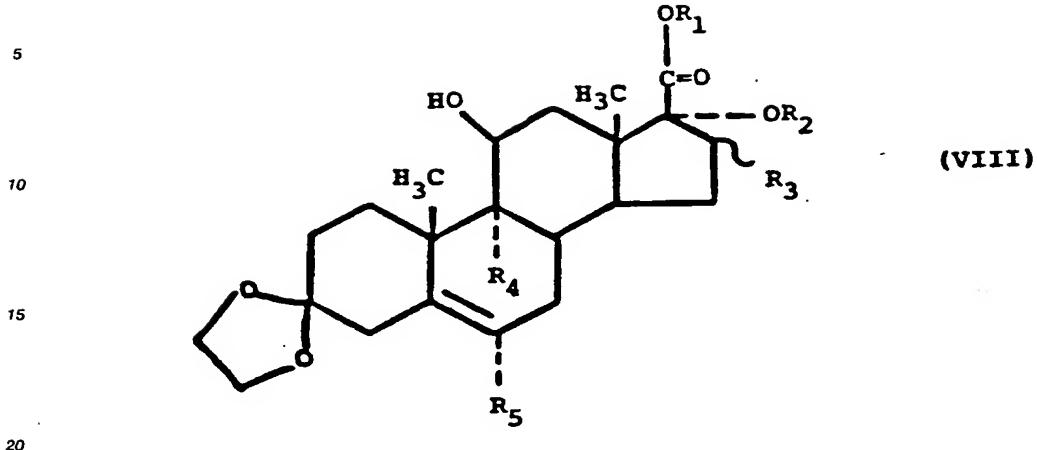


45 where R_3 is hydrogen, α -methyl, β -methyl, α - OR_2 or β - OR_2 , and R_1 , R_4 and R_5 are as defined in (a) above;

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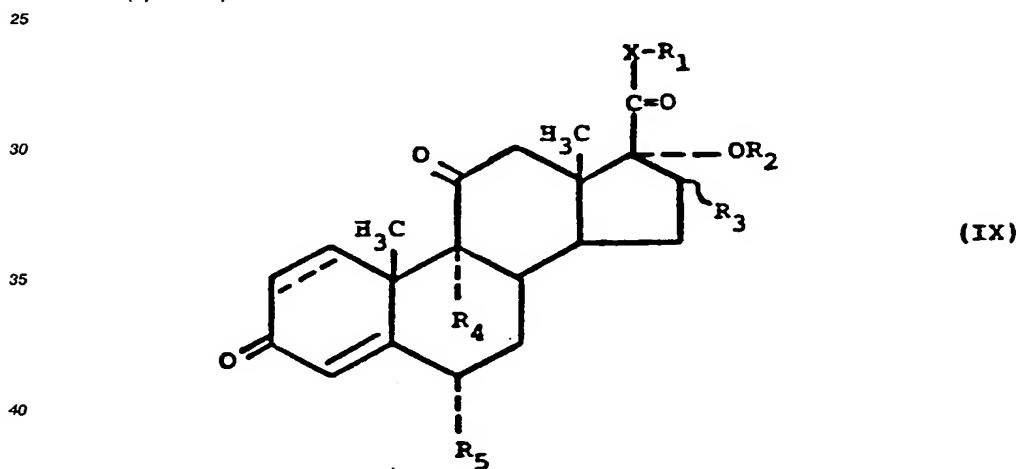
55

(g) A compound of the formula



wherein R₃ is hydrogen, α -methyl, β -methyl, α -OR₂ or β -OR₂, and R₁, R₂, R₄ and R₅ are as defined in (a) above;

(h) a compound of the formula



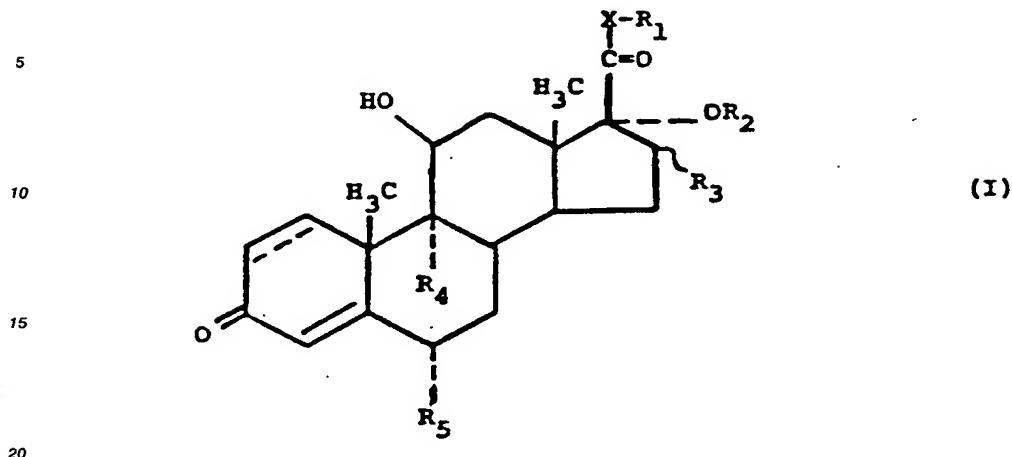
45 wherein R₁, R₂, R₃, R₄, R₅, X and the dotted line in ring A are as defined in (a) above.

2. A compound selected from the group consisting of:

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(a) a compound of the formula



wherein:

R_1 is C_1-C_6 alkyl; C_1-C_6 (monohalo or polyhalo)alkyl; $-CH_2COOR_6$ wherein R_6 is C_1-C_6 alkyl; $-CH_2-Y-(C_1-C_6$ alkyl) wherein Y is $-S-$, $-SO-$, $-SO_2-$ or $-O-$; or

wherein R_6' is C_1-C_6 alkyl or phenyl;

R_2 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl;

R_3 is hydrogen, α -hydroxy, α -methyl, β -methyl or

wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen or fluoro;

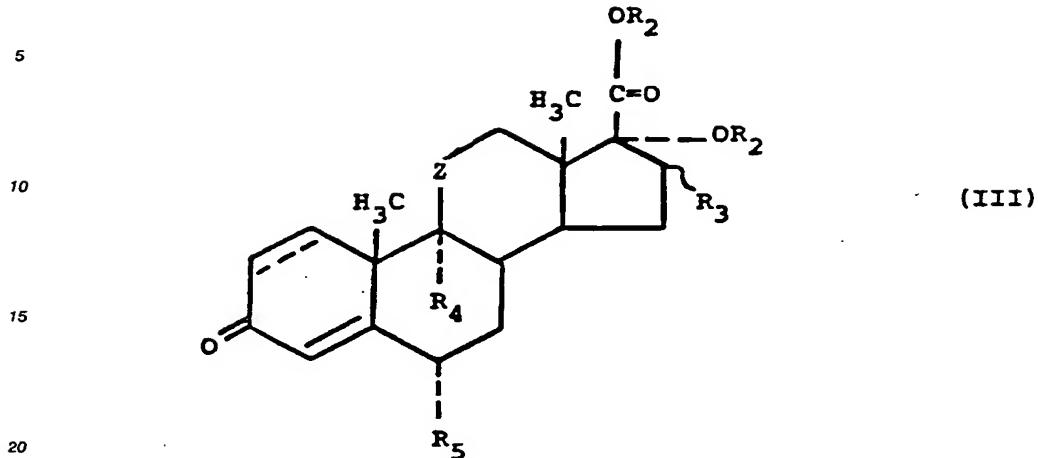
R_5 is hydrogen or fluoro;

X is $-O-$ or $-S-$;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated;

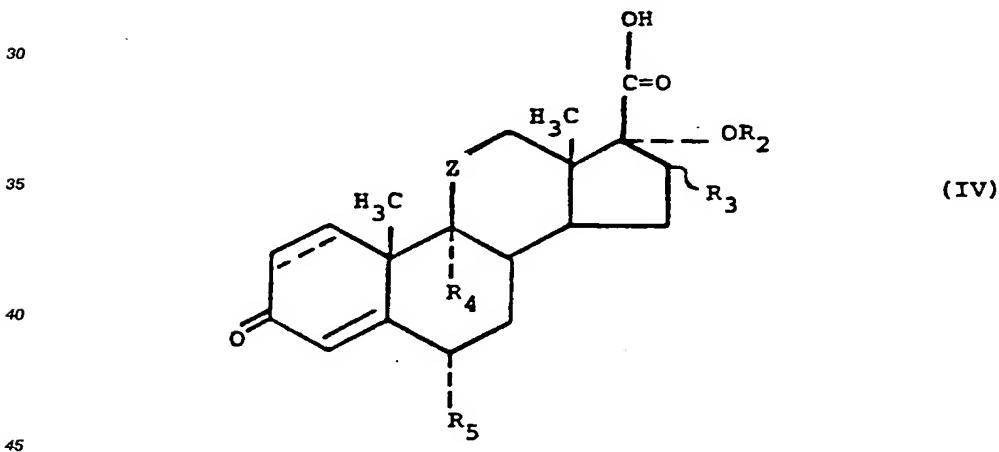
(b) a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group;

(c) a compound of the formula



25 wherein R_2 , R_4 , R_5 , and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β -hydroxymethylene and R_3 is hydrogen, α -methyl, β -methyl, $=CH_2$ or α - or β - OR_2 wherein R_2 is identical to R_2 above;

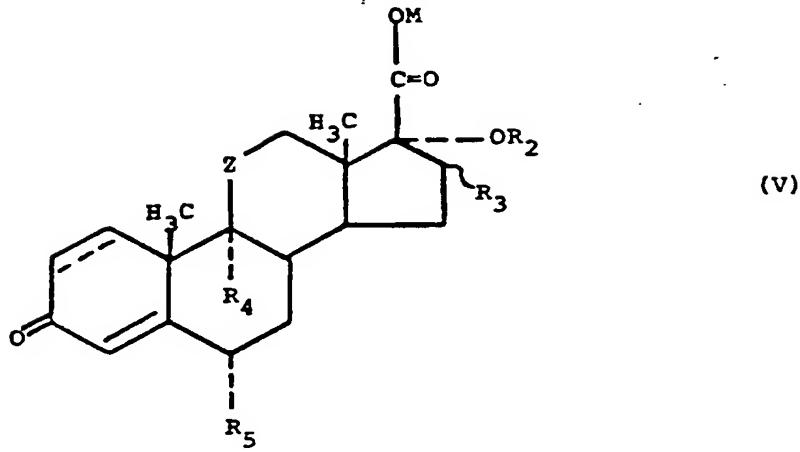
(d) a compound of the formula



50 wherein R_2 , R_4 , R_5 , and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β -hydroxymethylene and R_3 is hydrogen, α -methyl, β -methyl, $=CH_2$ or α - or β - OR_2 wherein R_2 is identical to R_2 above;

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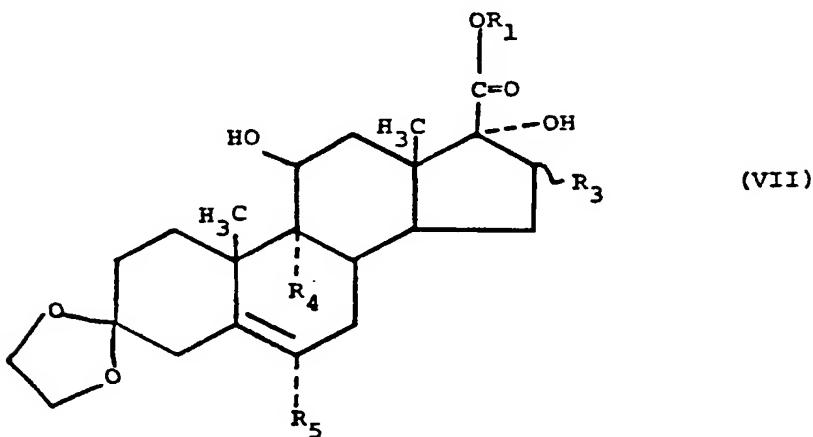
(e) a compound of the formula



wherein M is alkali metal, thallium, alkaline earth metal/2 or NH_4 and R_2 , R_3 , R_4 , R_5 , Z and the dotted line in ring A are as defined in (a) and (d) above;

(f) compound of the formula

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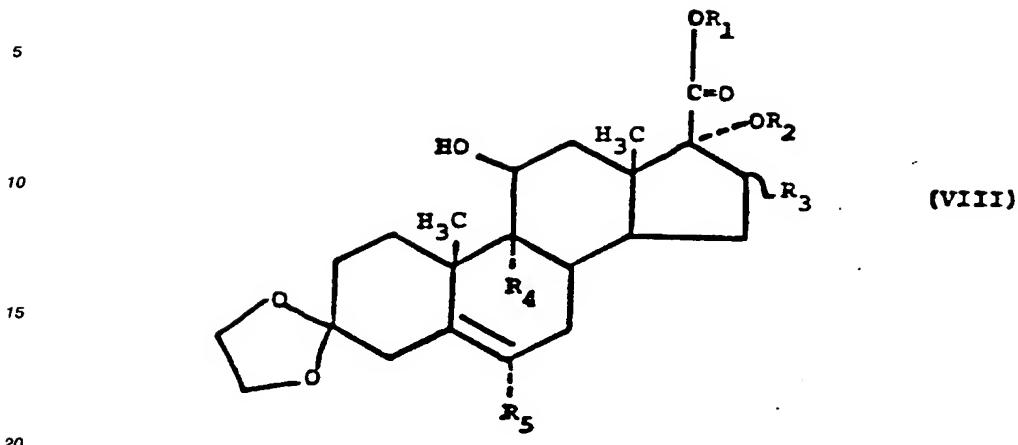
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wherein R_3 is hydrogen, α -methyl, β -methyl, α - OR_2 or β - OR_2 , and R_1 , R_4 and R_5 are as defined in (a) above;

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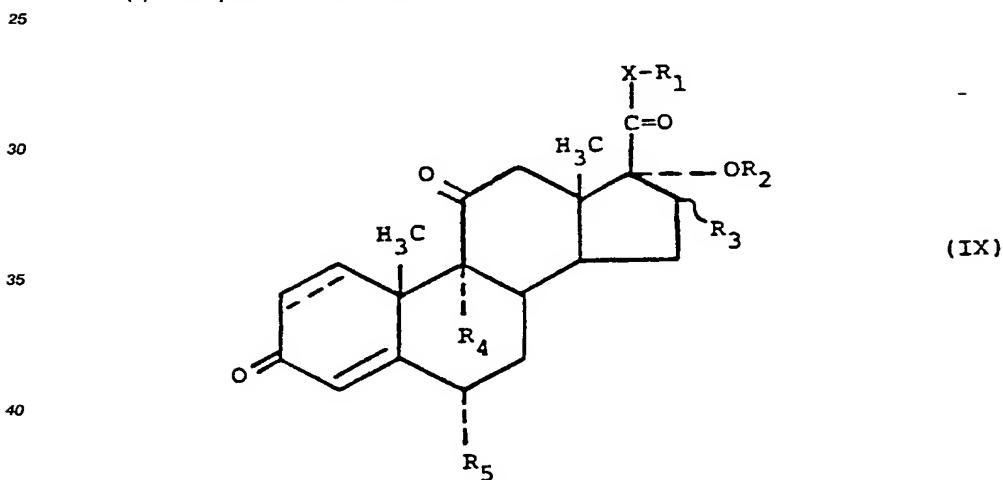
55

(g) a compound of the formula



wherein R₃ is hydrogen, α -methyl, β -methyl, α -OR₂ or β -OR₂, and R₁, R₂, R₄ and R₅ are as defined in (a) above;

(h) a compound of the formula



wherein R₁, R₂, R₃, R₄, R₅, X and the dotted line in ring A are as defined in (a) above.

3. A compound of Claim 1 or 2, said compound being a quaternary ammonium salt of a compound of formula (I) wherein at least one of R₁ and R₂ is a halo-substituted alkyl group.
4. A compound of Claim 1, said compound having the structural formula (I) wherein R₃ is hydrogen, α -methyl, β -methyl, $=\text{CH}_2$, α -OR₂ or β -OR₂.
5. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R₁ is C₁-C₆ alkyl or C₁-C₆ (monohalo or polyhalo)alkyl.
- 55 6. A compound of Claim 5 wherein C₁-C₆ monochloroalkyl is chloromethyl.
7. A compound of at least one of the preceding claims wherein R₂ is C₁-C₆ alkyl or C₁-C₆ monohaloalkyl.

8. A compound of at least one of the preceding claims wherein R₂ is C₃-C₈ cycloalkyl, phenyl, benzyl or C₁-C₆ (monohalo or polyhalo)alkyl.

9. A compound of at least one of the preceding claims, said compound having the structural formula (I) wherein X is -O-.

10. A compound of at least one of the preceding claims wherein R₄ and R₅ are hydrogen.

11. A compound of at least one of the preceding claims wherein at least one of R₄ and R₅ is fluoro.

12. A compound of at least one of the preceding claims wherein R₄ is fluoro and R₅ is hydrogen.

13. A compound of at least one of the preceding claims wherein R₃ is α -methyl or β -methyl.

14. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R₁ is -CH₂COOR₆, -CH₂-Y-(C₁-C₆ alkyl),



or -CH₂CONR₇R₈.

25 15. A compound of Claim 14 wherein at least one of R₇ and R₈ is hydrogen or C₁-C₆ alkyl.

16. A compound of Claim 14 wherein R₇ and R₈ are combined so that -NR₇R₈ represents the residue of a saturated monocyclic secondary amine containing 5 to 7 carbon atoms.

30 17. A compound of Claim 16 wherein -NR₇R₈ represents morpholino, 1-pyrrolidinyl, 4-benzyl-1-piperazinyl, perhydro-1,2,4-oxathiazin-4-yl, 1- or 4-piperazinyl, 4-methyl-1-piperazinyl, piperidino, hexamethyleneimino, 4-phenylpiperidino, 2-methyl-1-pyrazolidinyl, 1- or 2-pyrazolidinyl, 3-methyl-1-imidazolidinyl, 1- or 3-imidazolidinyl, 4-benzylpiperidino or 4-phenyl-1-piperazinyl.

35 18. A compound of Claim 1, said compound having the structural formula (I) wherein R₁ is



wherein R₉ is hydrogen or methyl, or wherein R₉ and the lower alkyl group adjacent to Y are combined so that R₁ is



wherein Y is -S-, -SO-, -SO₂ - or -O- and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms.

50 19. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein the R₃, R₄ and R₅ groupings and the 1,2-linkage are identical to those of a glucocorticosteroid selected from the group consisting of hydrocortisone, prednisolone, fludrocortisone, betamethasone, dexamethasone, flumethasone, fluprednisolone, methyl prednisolone and paramethasone.

55 20. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R₃ is α -OR₂, and wherein the R₄ and R₅ groupings and the 1,2-linkage are identical to those of triamcinolone.

21. A compound of Claim 1 or 2, said compound having the structural formula (III), (IV) or (VIII) wherein Z is β -hydroxymethylene and R₂ is C₁-C₆ alkyl.

22. A compound of Claim 1 or 2, said compound having the structural formula (VII) wherein Z is β -hydroxymethylene and R₁ is C₁-C₆ alkyl or C₁-C₆ monohaloalkyl.

23. A compound of Claim 1 or 2, said compound having the structural formula (IX) wherein R₁ is C₁-C₆ - (monohalo or polyhalo)alkyl.

24. A compound of Claim 23 wherein R₂ is C₁-C₆ alkyl.

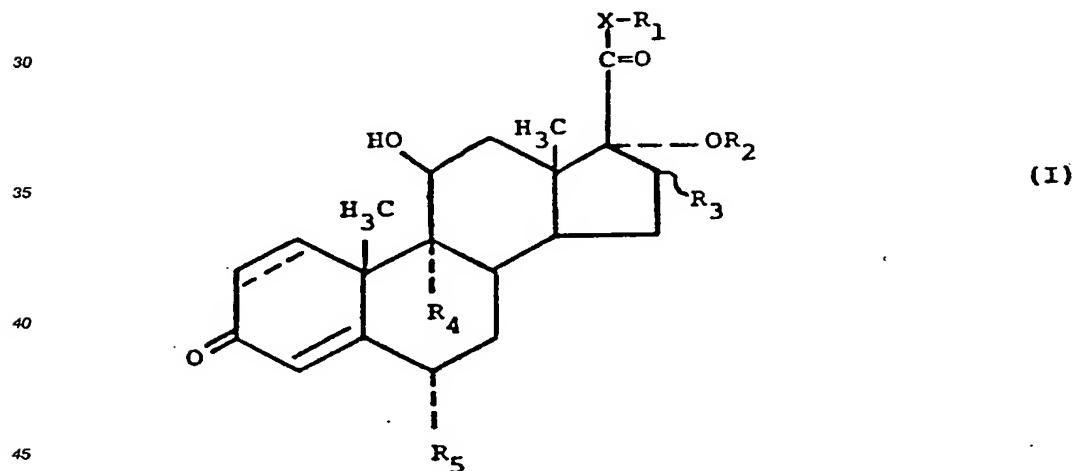
25. A compound of Claim 1 or 2, said compound having the structural formula (IX) wherein R₁ is C₁-C₆ alkyl or C₁-C₆ monohaloalkyl, R₂ is C₁-C₆ alkyl or C₁-C₆ monohaloalkyl and X is -O-.

26. A compound of Claim 25 wherein the R₃, R₄ and R₅ groupings and the 1,2-linkage are identical to those of a glucocorticosteroid selected from the group consisting of cortisone, prednisone, chloroprednisone and meprednisone.

27. A pharmaceutical composition of matter comprising an anti-inflammatory effective amount of a compound of at least one of the preceding claims, in combination with a non-toxic pharmaceutically acceptable carrier therefor suitable for topical or other local application.

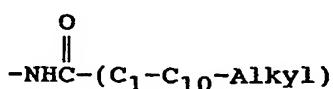
Patentansprüche

28. 1. Verbindung, ausgewählt aus der Gruppe, die besteht aus:
(a) einer Verbindung der Formel:

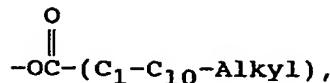


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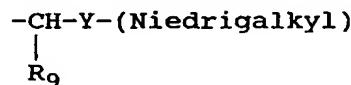
50 R₁ C₁-C₁₀-Alkyl, C₂-C₁₀-(Monohydroxy- oder Polyhydroxy)alkyl, C₁-C₁₀-(Monohalogen- oder Polyhalogen)alkyl oder -CH₂COOR₆ bedeutet, worin R₆ unsubstituiertes oder substituiertes C₁-C₁₀-Alkyl, C₃-C₈-Cycloalkyl, C₃-C₈-Cycloalkenyl oder C₂-C₁₀-Alkenyl bedeutet, wobei die Substituenten ausgewählt werden aus der Gruppe, die besteht aus Halogen, Niedrigalkoxy, Niedrigalkylthio, Niedrigalkylsulfinyl, Niedrigalkylsulfonyl.



und



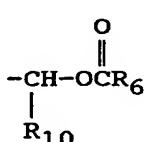
oder worin R_6 unsubstituiertes oder substituiertes Phenyl oder Benzyl bedeutet, wobei die Substituenten ausgewählt werden aus der Gruppe, die besteht aus Niedrigalkyl, Niedrigalkoxy, Halogen, 10 Carbamoyl, Niedrigalkoxycarbonyl, Niedrigalkanoyloxy, Niedrigalkylthio, Mono(niedrigalkyl)-amino, Di(niedrigalkyl)amino, Mono(niedrigalkyl)carbamoyl, Di(niedrigalkyl)carbamoyl, Niedrigalkylthio, Niedrigalkylsulfinyl und Niedrigalkylsulfonyl; oder R_1 - $CH_2CONR_7R_8$ bedeutet, worin R_7 und R_8 , die gleich oder unterschiedlich sind, je Wasserstoff, Niedrigalkyl, C_3-C_8 -Cycloalkyl, Phenyl oder 15 Benzyl bedeuten oder worin R_7 und R_8 so kombiniert sind, daß $-NR_7R_8$ einen Rest eines gesättigten monocyclischen sekundären Amins bedeutet; oder worin R_1 unsubstituiertes oder substituiertes Phenyl oder Benzyl bedeutet, wobei die Substituenten ausgewählt werden aus der Gruppe Phenyl- und Benzyl-Substituenten, wie sie oben unter Bezugnahme auf R_6 definiert wurden; oder worin R_1



25 bedeutet, worin Y -S-, -SO-, SO_2 - oder -O- bedeutet und R_9 Wasserstoff, Niedrigalkyl oder Phenyl bedeutet, oder worin R_9 und die Niedrigalkylgruppe, die benachbart zu Y ist, so kombiniert sind, daß R_1 ein cyclisches System des Typs

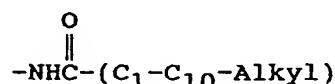


35 bedeutet, worin Y die oben gegebene Definition besitzt und die Alkylengruppe 3 bis 10 Kohlenstoffatome enthält, wovon mindestens 3 und nicht mehr als 6 Ringatome sind; oder worin R_1



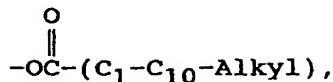
45 bedeutet, worin R_6 die oben gegebene Definition besitzt und R_{10} Wasserstoff, Niedrigalkyl, Phenyl oder Halogenphenyl bedeutet;

45 R_2 unsubstituiertes oder substituiertes C_1-C_{10} -Alkyl, C_3-C_8 -Cycloalkyl, C_3-C_8 -Cycloalkenyl oder C_2-C_{10} -Alkenyl bedeutet, wobei die Substituenten ausgewählt werden aus der Gruppe, die besteht aus Halogen, Niedrigalkoxy, Niedrigalkylthio, Niedrigalkylsulfinyl, Niedrigalkylsulfonyl,



und

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oder worin R_2 unsubstituiertes oder substituiertes Phenyl oder Benzyl bedeutet, wobei die Substituenten ausgewählt werden aus der Gruppe, die besteht aus Niedrigalkyl, Niedrigalkoxy, Halogen, Carbamoyl, Niedrigalkoxycarbonyl, Niedrigalkanoyloxy, Niedrighalogenalkyl, Mono(niedrigalkyl)-amino, Di(niedrigalkyl)amino, Mono(niedrigalkyl)carbamoyl, Di(niedrigalkyl)carbamoyl, Niedrigalkylthio, Niedrigalkylsulfinyl und Niedrigalkylsulfonyl;

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R_3 Wasserstoff, α -Hydroxy, β -Hydroxy, α -Methyl, β -Methyl, $=\text{CH}_2$ oder α - oder β - OR_2 bedeutet, worin R_2 identisch ist mit R_2 , wie es oben definiert wurde;

R_4 Wasserstoff, Fluor oder Chlor bedeutet;

R_5 Wasserstoff, Fluor, Chlor oder Methyl bedeutet;

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X -O- oder -S- bedeutet; und die gestrichelte Linie im Ring A anzeigen, daß die 1,2-Bindung gesättigt oder ungesättigt sein kann;

(b) einem quaternären Ammoniumsalz einer Verbindung der Formel (I), worin mindestens einer der Substituenten R_1 und R_2 eine Halogen-substituierte Alkylgruppe bedeutet;

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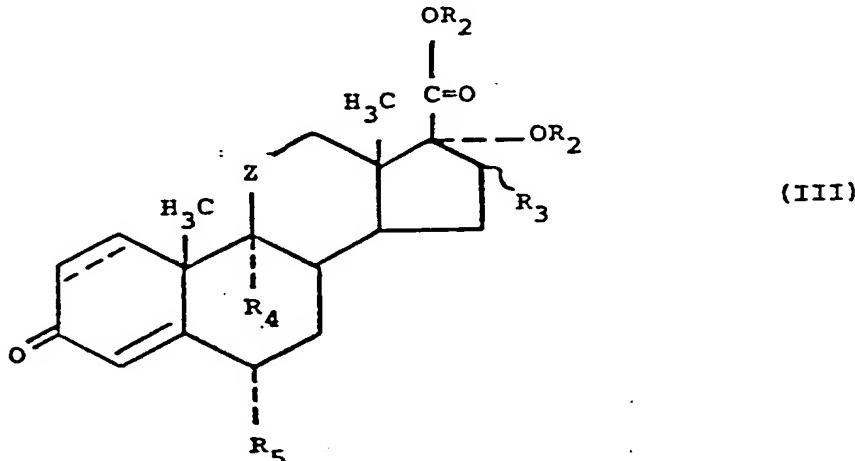
(c) einer Verbindung der Formel:

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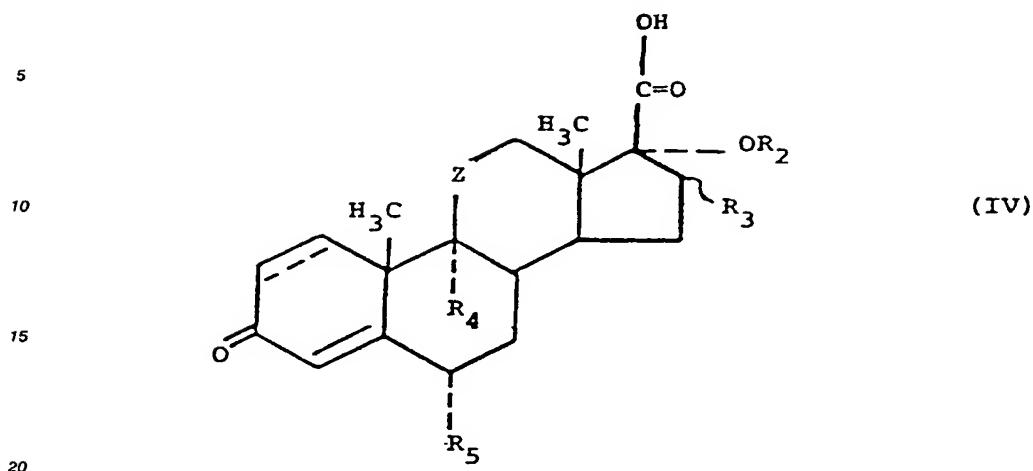
worin R_2 , R_4 , R_5 und die gestrichelte Linie im Ring A die oben bei (a) gegebenen Definitionen besitzen, Z Carbonyl oder β -Hydroxymethylen bedeutet und R_3 Wasserstoff, α -Methyl, β -Methyl, $=\text{CH}_2$ oder α - oder β - OR_2 bedeutet, worin R_2 identisch mit R_2 oben ist;

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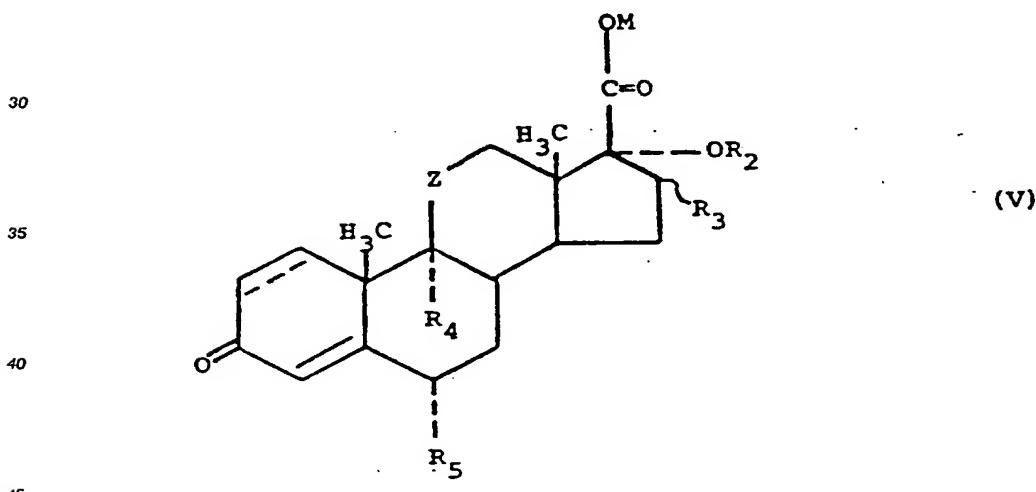
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(d) einer Verbindung der Formel:



worin R_2 , R_4 , R_5 und die gestrichelte Linie im Ring A die oben bei (a) gegebenen Definitionen besitzen, Z Carbonyl oder β -Hydroxymethylen bedeutet und R_3 Wasserstoff, α -Methyl, β -Methyl, $=CH_2$ oder α - oder β -OR₂ bedeutet, worin R₂ identisch mit R₂ oben ist;

(e) einer Verbindung der Formel:

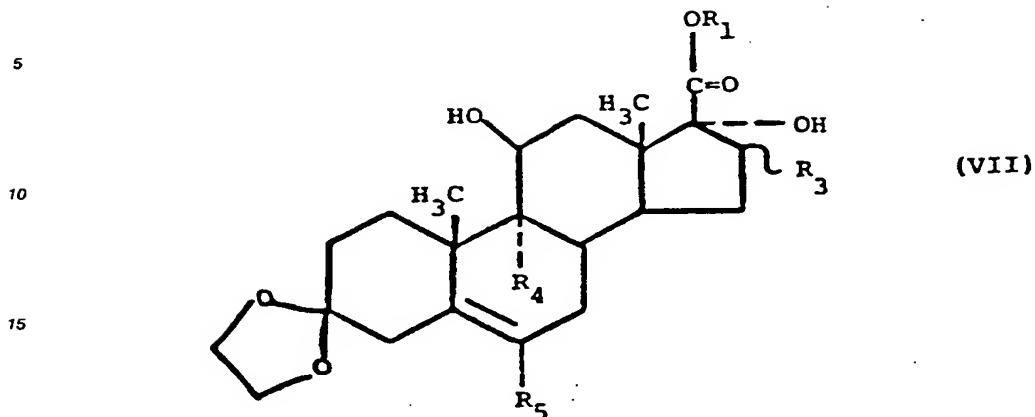


worin M ein Alkalimetall, Thallium, ein Erdalkalimetall/2 oder NH₄ bedeutet und R₂, R₃, R₄, R₅, Z und die gestrichelte Linie im Ring A die oben bei (a) und (d) gegebenen Definitionen besitzen;

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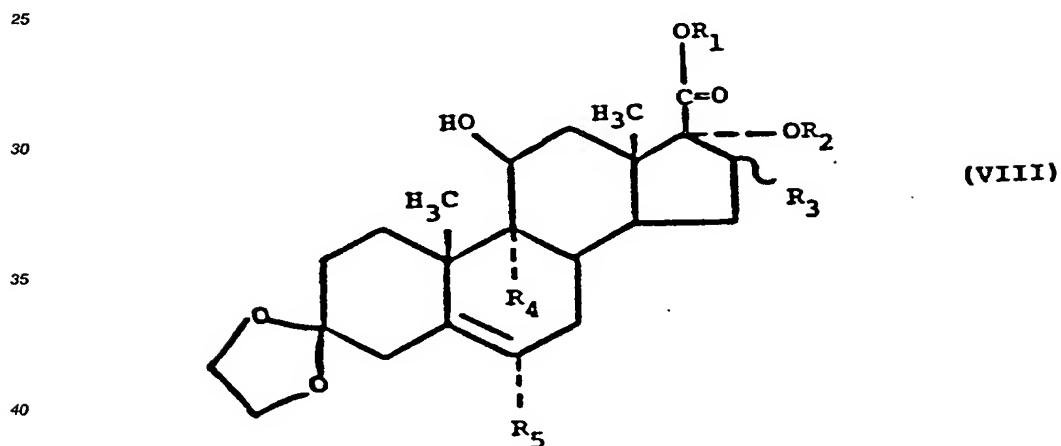
55

(f) einer Verbindung der Formel:



worin R_3 Wasserstoff, α -Methyl, β -Methyl, α -OR₂ oder β -OR₂ bedeutet und R₁, R₄ und R₅ die oben bei (a) gegebenen Definitionen besitzen;

(g) einer Verbindung der Formel:



worin R_3 Wasserstoff, α -Methyl, β -Methyl, α -OR₂ oder β -OR₂ bedeutet und R₁, R₂, R₄ und R₅ die bei (a) oben gegebenen Definitionen besitzen;

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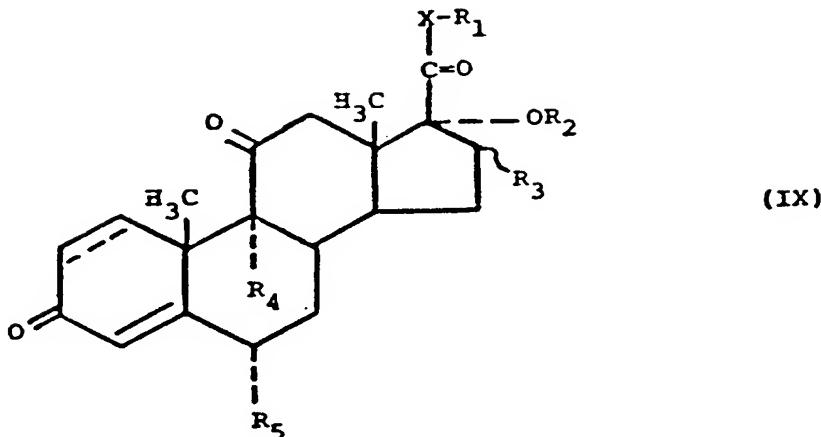
(h) einer Verbindung der Formel:

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worin R_1 , R_2 , R_3 , R_4 , R_5 , X und die gestrichelte Linie im Ring A die oben bei (a) gegebenen Definitionen besitzen.

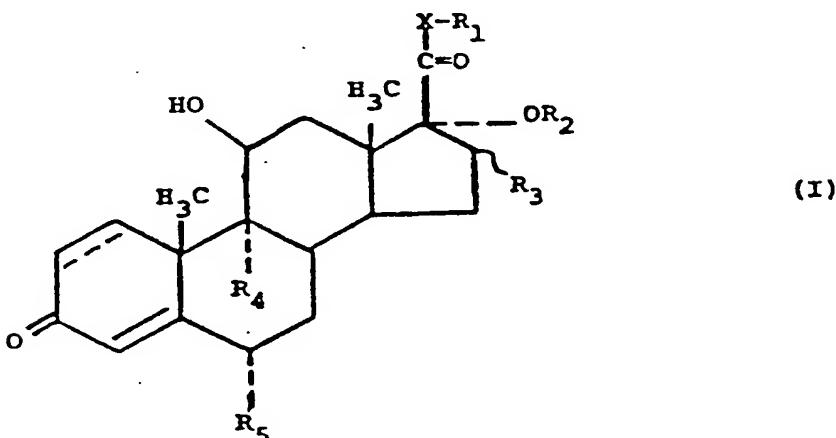
25 2. Verbindung, ausgewählt aus der Gruppe, die besteht aus:
(a) einer Verbindung der Formel:

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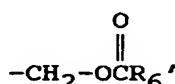
45



worin

R_1 C_1 - C_6 -Alkyl, C_1 - C_6 (Monohalogen- oder Polyhalogen)alkyl, $-CH_2COOR_6$, worin R_6 C_1 - C_6 -Alkyl, $-CH_2Y-(C_1-C_6\text{-Alkyl})$ bedeutet, worin Y $-S-$, $-SO-$, $-SO_2-$ oder $-O-$ bedeutet, oder

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bedeutet, worin R_6 , C_1 - C_6 -Alkyl oder Phenyl bedeutet;

R_2 C_1 - C_6 -Alkyl, C_3 - C_8 -Cycloalkyl, Phenyl, Benzyl oder C_1 - C_6 -(Monohalogen- oder Polyhalogen)-alkyl bedeutet;

R₃ Wasserstoff, α -Hydroxy, α -Methyl, β -Methyl oder



bedeutet, worin R₂ identisch ist mit R₂, wie es oben definiert wurde;

R₄ Wasserstoff oder Fluor bedeutet;

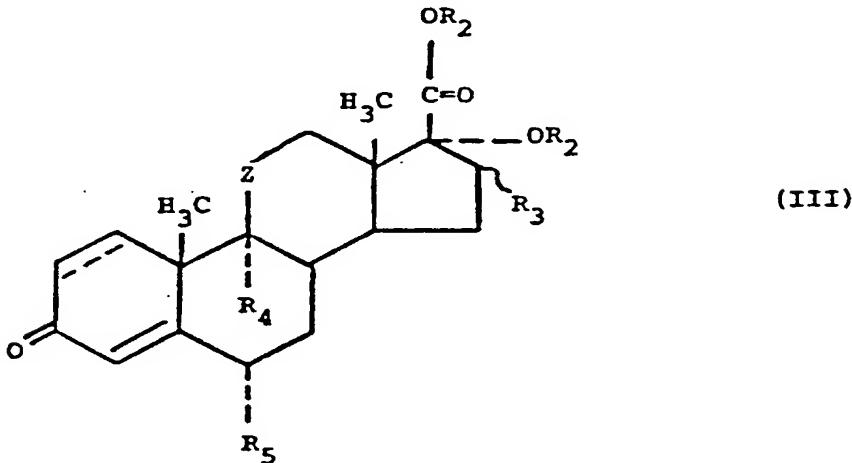
10 R₅ Wasserstoff oder Fluor bedeutet;

X -O- oder -S- bedeutet;

und die gestrichelte Linie im Ring A anzeigt, daß die 1,2-Bindung gesättigt oder ungesättigt ist;

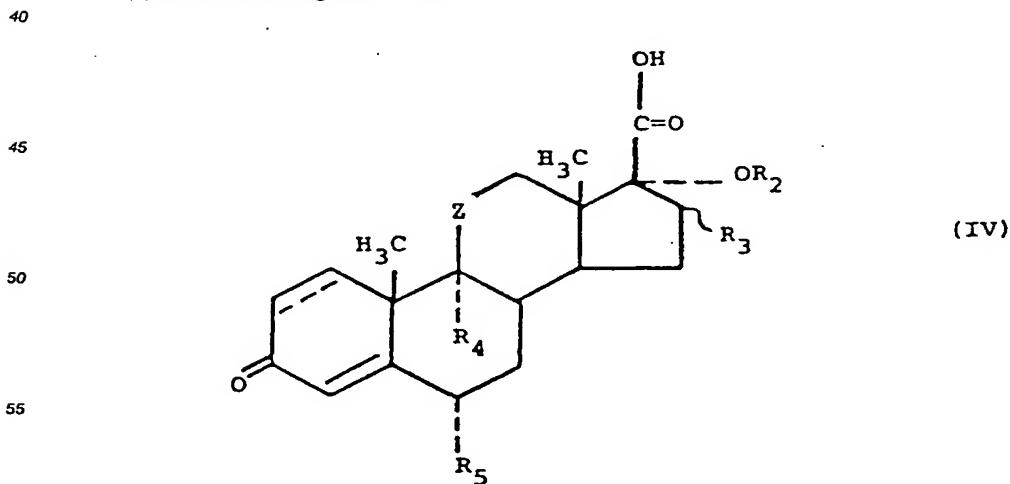
(b) einem quaternären Ammoniumsalz einer Verbindung der Formel (I), worin mindestens einer der Substituenten R₁ und R₂ eine Halogen-substituierte Alkylgruppe bedeutet;

15 (c) einer Verbindung der Formel:



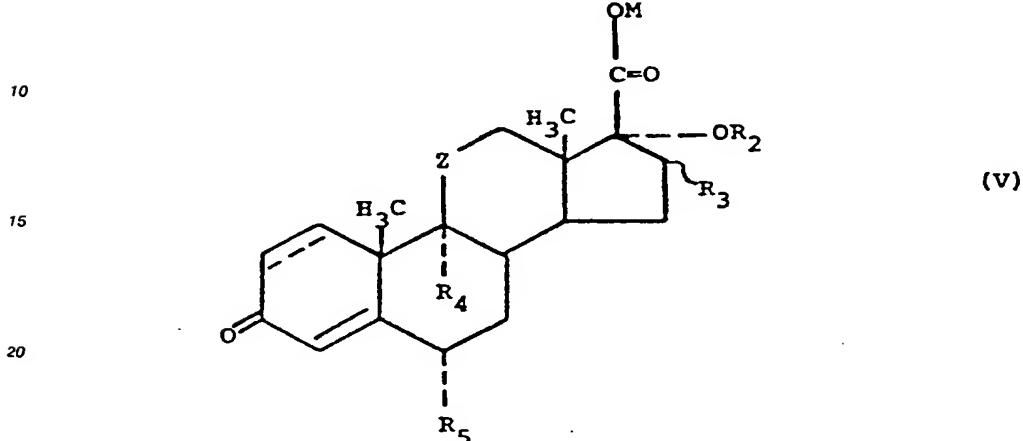
worin R₂, R₄, R₅ und die gestrichelte Linie im Ring A die oben bei (a) gegebenen Definitionen besitzen, Z Carbonyl oder β -Hydroxymethyl bedeutet und R₃ Wasserstoff, α -Methyl, β -Methyl, =CH₂ oder α - oder β -OR₂ bedeutet, worin R₂ identisch mit R₂ oben ist;

(d) einer Verbindung der Formel:



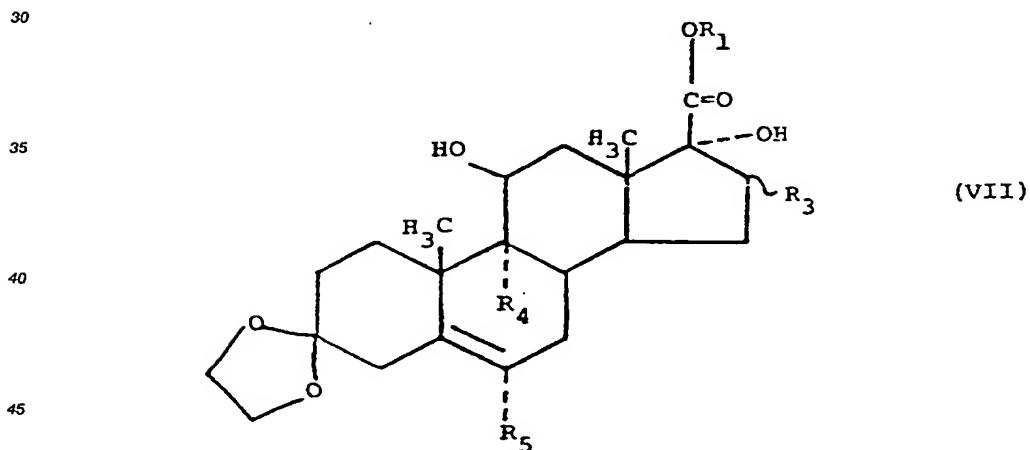
worin R_2 , R_4 , R_5 und die gestrichelte Linie im Ring A die oben bei (a) gegebenen Definitionen besitzen, Z Carbonyl oder β -Hydroxymethylen bedeutet und R_3 Wasserstoff, α -Methyl, β -Methyl, $=CH_2$ oder α - oder β - OR_2 bedeutet, worin R_2 identisch mit R_2 oben ist;
(e) einer Verbindung der Formel:

5



worin M ein Alkalimetall, Thallium, ein Erdalkalimetall/2 oder NH_4 bedeutet und R_2 , R_3 , R_4 , R_5 , Z und die gestrichelte Linie im Ring A die oben bei (a) und (d) gegebenen Definitionen besitzen;
(f) einer Verbindung der Formel:

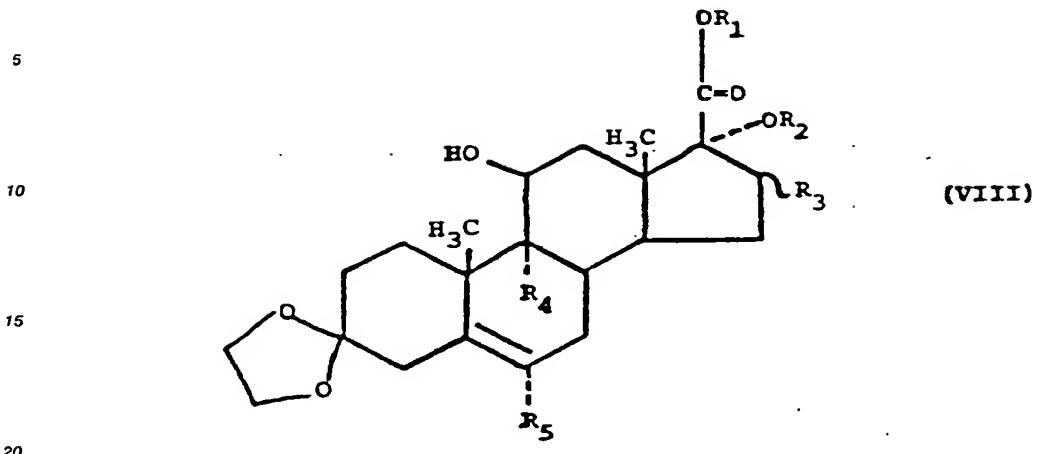
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worin R_3 Wasserstoff, α -Methyl, β -Methyl, α - OR_2 oder β - OR_2 bedeutet und R_1 , R_4 und R_5 die oben bei (a) gegebenen Definitionen besitzen;

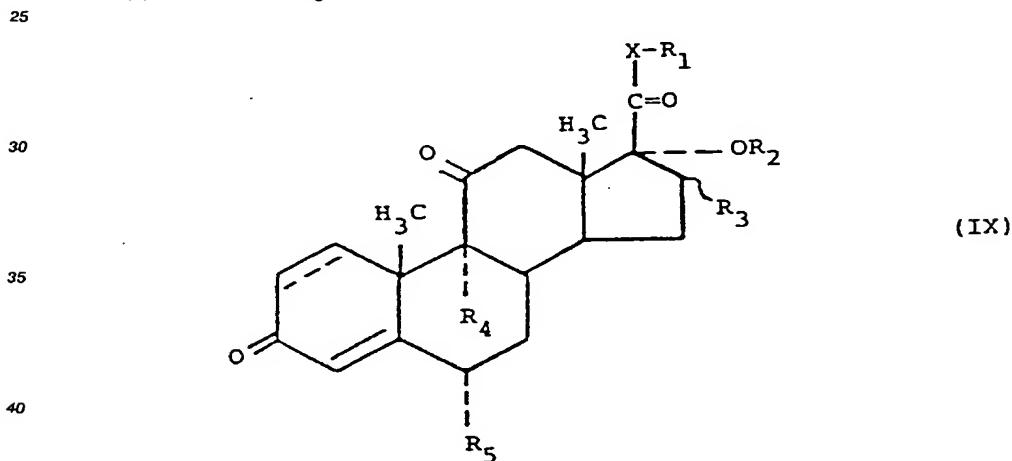
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(g) einer Verbindung der Formel:



worin R_3 Wasserstoff, α -Methyl, β -Methyl, α -OR₂ oder β -OR₂ bedeutet und R_1 , R_2 , R_4 und R_5 die bei (a) oben gegebenen Definitionen besitzen;

(h) einer Verbindung der Formel:



worin R_1 , R_2 , R_3 , R_4 , R_5 , X und die gestrichelte Linie im Ring A die oben bei (a) gegebenen Definitionen besitzen.

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3. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung ein quaternäres Ammoniumsalz einer Verbindung der Formel (I) ist, worin mindestens einer der Substituenten R_1 und R_2 eine Halogen-substituierte Alkylgruppe bedeutet.
4. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß die Verbindung die Strukturformel (I) besitzt, worin R_3 Wasserstoff, α -Methyl, β -Methyl, =CH₂, α -OR₂ oder β -OR₂ bedeutet.
5. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung die Strukturformel (I) besitzt, worin R_1 C₁-C₆-Alkyl oder C₁-C₆-(Monohalogen- oder Polyhalogen)alkyl bedeutet.
6. Verbindung nach Anspruch 5, dadurch gekennzeichnet, daß C₁-C₆-Monochloralkyl Chlormethyl bedeutet.

7. Verbindung nach mindestens einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß R₂ C₁-C₄-Alkyl oder C₁-C₆-Monohalogenalkyl bedeutet.

8. Verbindung nach mindestens einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß R₂ C₃-C₈-Cycloalkyl, Phenyl, Benzyl oder C₁-C₆-(Monohalogen- oder Polyhalogen)alkyl bedeutet.

9. Verbindung nach mindestens einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß die Verbindung die Strukturformel (I) aufweist, worin X -O-bedeutet.

10. Verbindung nach mindestens einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß R₄ und R₅ Wasserstoff bedeuten.

11. Verbindung nach mindestens einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß mindestens einer von R₄ und R₅ Fluor bedeutet.

12. Verbindung nach mindestens einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß R₄ Fluor und R₅ Wasserstoff bedeuten.

13. Verbindung nach mindestens einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß R₃ α -Methyl oder β -Methyl bedeutet.

14. Verbindung nach Anspruch 1 oder 2, dadurch **gekennzeichnet**, daß die Verbindung die Strukturformel (I) besitzt, worin R₁ -CH₂COOR₆, -CH₂-Y-(C₁-C₆-Alkyl),



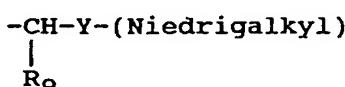
30 oder -CH₂CONR₇R₈ bedeutet.

15. Verbindung nach Anspruch 14, dadurch **gekennzeichnet**, daß mindestens einer der Substituenten R₇ und R₈ Wasserstoff oder C₁-C₆-Alkyl bedeutet.

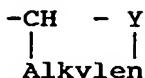
35 16. Verbindung nach Anspruch 14, dadurch **gekennzeichnet**, daß R₇ und R₈ so gebunden sind, daß -NR₇R₈ den Rest eines gesättigten monocyclischen sekundären Amins, der 5 bis 7 Kohlenstoffatome enthält, bedeutet.

40 17. Verbindung nach Anspruch 16, dadurch **gekennzeichnet**, daß -NR₇R₈ Morpholino, 1-Pyrrolidinyl, 4-Benzyl-1-piperazinyl, Perhydro-1,2,4-oxathiazin-4-yl, 1- oder 4-Piperazinyl, 4-Methyl-1-piperazinyl, Piperidino, Hexamethylenimino, 4-Phenylpiperidino, 2-Methyl-1-pyrazolidinyl, 1- oder 2-Pyrazolidinyl, 3-Methyl-1-imidazolidinyl, 1- oder 3-Imidazolidinyl, 4-Benzylpiperidino oder 4-Phenyl-1-piperazinyl bedeutet.

45 18. Verbindung nach Anspruch 1, dadurch **gekennzeichnet**, daß die Verbindung die Strukturformel (I) besitzt, worin R₁



bedeutet, worin R₉ Wasserstoff oder Methyl bedeutet, oder worin R₉ und die Niedrigalkylgruppe, die benachbart zu Y ist, so kombiniert sind, daß R₁ ein



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bedeutet, worin Y -S-, -SO-, -SO₂- oder -O- bedeutet und die Alkylengruppe 3 bis 10 Kohlenstoffatome enthält, wovon mindestens 3 und nicht mehr als 6 Ringatome sind.

10 19. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung die Strukturformel (I) besitzt, worin die R₃-, R₄- und R₅-Gruppen und die 1,2-Bindung identisch sind wie jene eines Glucocorticosteroids, ausgewählt aus der Gruppe, die besteht aus Hydrocortison, Prednisolon, Fludrocortison, Betamethason, Dexamethason, Flumethason, Fluprednisolon, Methylprednisolon und Paramethason.

15 20. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung die Strukturformel (I) besitzt, worin R₃ α -OR₂ bedeutet und worin die R₄- und R₅-Gruppen und die 1,2-Bindung identisch sind wie die von Triamcinolon.

20 21. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung die Strukturformel (III), (IV) oder (VIII) besitzt, worin Z β -Hydroxymethylen und R₂ C₁-C₆-Alkyl bedeuten.

25 22. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung die Strukturformel (VII) besitzt, worin Z β -Hydroxymethylen bedeutet und R₁ C₁-C₆-Alkyl oder C₁-C₆-Monohalogenalkyl bedeutet.

23. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung die Strukturformel (IX) besitzt, worin R₁ C₁-C₆-(Monohalogen- oder Polyhalogen)alkyl bedeutet.

30 24. Verbindung nach Anspruch 23, dadurch gekennzeichnet, daß R₂ C₁-C₆-Alkyl bedeutet.

25 25. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung die Strukturformel (IX) besitzt, worin R₁ C₁-C₆-Alkyl oder C₁-C₆-Monohalogenalkyl bedeutet, R₂ C₁-C₆-Alkyl oder C₁-C₆-Monohalogenalkyl bedeutet und X -O- bedeutet.

35 26. Verbindung nach Anspruch 25, dadurch gekennzeichnet, daß die R₃-, R₄- und R₅-Gruppen und die 1,2-Bindung identisch sind mit denen eines Glucocorticosteroids, ausgewählt aus der Gruppe, die besteht aus Cortison, Prednison, Chlorprednison und Meprednison.

40 27. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es eine antiinflammatorisch wirksame Menge einer Verbindung von mindestens einem der vorhergehenden Ansprüche zusammen mit einem nichttoxischen, pharmazeutisch annehmbaren Träger dafür enthält und für die topische oder eine andere lokale Anwendung geeignet ist.

Revendications

45 1. Composé choisi à partir du groupe constitué de :

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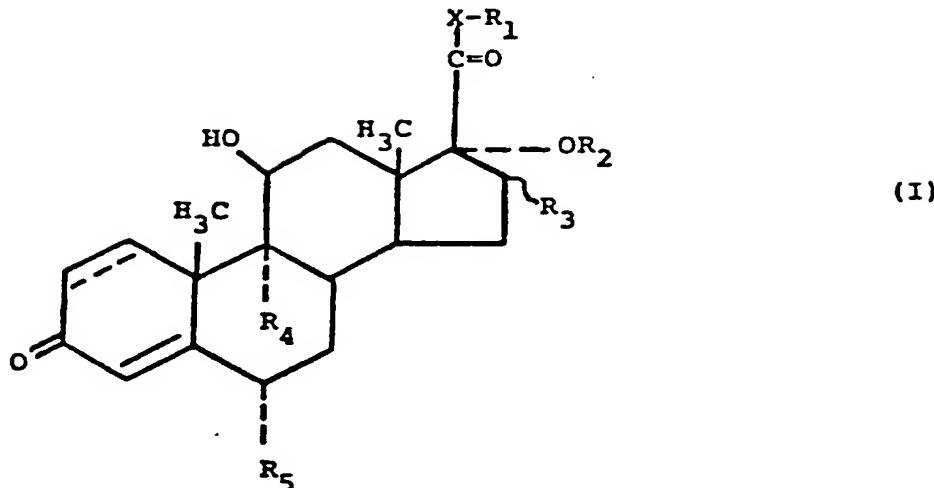
(a) un composé de formule

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dans laquelle :

25 R₁ est un alkyle de C₁-C₁₀ ; un (monohydroxy ou polyhydroxy)alkyle de C₂-C₁₀ ; un (monohalo ou polyhalo) alkyle de C₁-C₁₀ ; ou -CH₂COOR₆ où R₆ est un alkyle de C₁-C₁₀ substitué ou non substitué , un cycloalkyle de C₃-C₈ ,un cycloalkényle de C₃-C₈ ou un alkényle de C₂-C₁₀, les substituants étant choisis dans le groupe constitué de halo, alkoxy inférieur, alkylthio inférieur, alkylsulfinyle inférieur, alkylsulfuryle inférieur,

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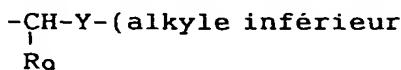
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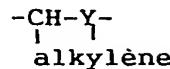
ou R₆ est un phényle ou un benzyle substitué ou non substitué, les substituants étant choisis dans le groupe constitué d' un alkyle inférieur, alkoxy inférieur, halo, carbamoyle, alkoxy carbonyle inférieur, alkanoyloxy inférieur, haloalkyle inférieur, mono(alkyle inférieur) amino, di (alkyle inférieur) amino, mono (alkyle inférieur) carbamoyle, di(alkyle inférieur) carbamoyle, alkylthio inférieur, alkylsulfinyle inférieur et alkylsulfuryle inférieur ; ou bien R₁ est -CH₂CONR₇R₈ dans lequel R₇ et R₈, qui peuvent être identiques ou différents, sont chacun un hydrogène, un alkyle inférieur, un cycloalkyle de C₃-C₈, un phényle ou un benzyle, ou bien R₇ et R₈ sont combinés de façon que -NR₇R₈ représente le résidu d'une amine secondaire monocyclique saturée ; ou R₁ est un phényle ou un benzyle substitué ou non substitué, les substituants étant choisis dans le groupe des substituants du phényle ou du benzyle définis ci-dessus par rapport à R₆ ; ou R₁ est

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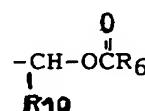
55 dans lequel Y est -S-, -SO-, -SO₂-ou -O- et R₉ est un hydrogène, un alkyle ou phényle inférieur, ou bien R₉ et le groupe alkyle adjacent à Y sont combinés de sorte que R₁ est un système cyclique du type



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dans lequel Y est défini comme ci-dessus et le groupe alkylène contient 3 à 10 atomes de carbone, dont au moins 3 et pas plus que 6 sont des atomes d'un cycle; ou bien R₁ est

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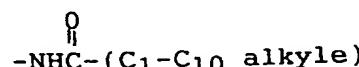


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dans lequel R₆ est défini comme ci-dessus et R₁₀ est un hydrogène, un alkyle inférieur, un phényle ou un halophényle ;

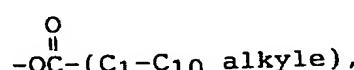
R₂ est un alkyle de C₁-C₁₀ substitué ou non substitué, un cycloalkyle de C₃-C₈, un cycloalkényle de C₃-C₈ ou un alkényle de C₂-C₁₀, les substituants étant choisis dans le groupe constitué de halo, alkoxy inférieur, alkylthio inférieur, alkylsulfinyle inférieur, alkylsulfuryle inférieur,

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et



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ou R₂ est un phényle ou un benzyle substitué ou non substitué, les substituants étant choisis dans le groupe constitué d'alkyle inférieur, alkoxy inférieur, halo, carbamoyle, alkoxy carbonyle inférieur, alkanoyloxy inférieur, haloalkyle inférieur, mono (alkyle inférieur) amino, di(alkyle inférieur) amino, mono (alkyle inférieur) carbamoyle, di (alkyle inférieur) carbamoyle, alkylthio inférieur, alkylsulfinyle inférieur et alkylsulfuryle inférieur;

R₃ est un hydrogène, α -hydroxy, β -hydroxy, α -méthyle, β -méthyle, =CH₂, ou α - ou β -OR₂ dans lequel R₂ est identique à R₂ comme défini ci-dessus ;

R₄ est un hydrogène, fluoro ou chloro ;

R₅ est un hydrogène, fluoro, chloro ou méthyle ;

X est -O- ou -S- ;

et la ligne en pointillé dans le cycle A indique que la liaison 1,2- est saturée ou non saturée ;

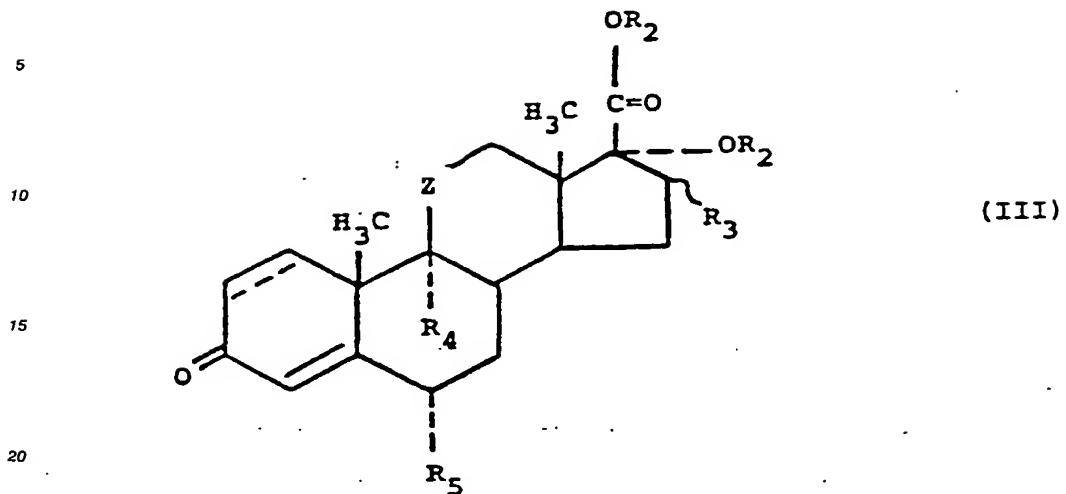
(b) un sel d'ammonium quaternaire d'un composé de formule (I) dans lequel au moins un des termes R₁ et R₂ est un groupe alkyle halo-substitué ;

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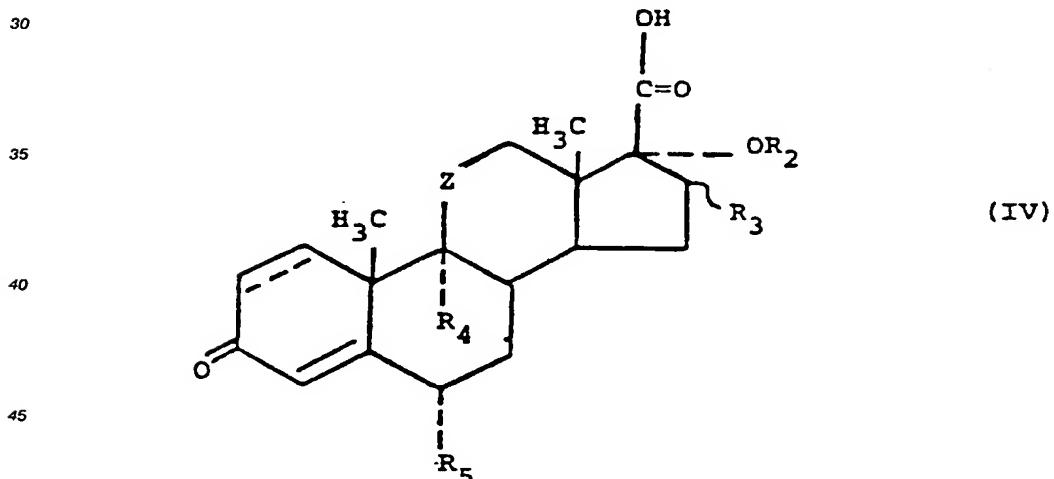
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(c) un composé de formule



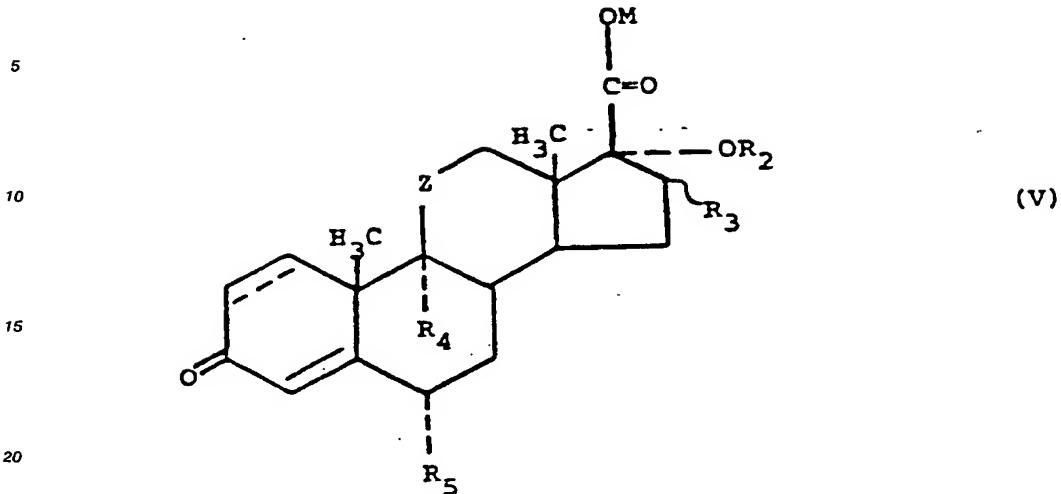
25 dans laquelle R₂, R₄, R₅, et la ligne en pointillé dans le cycle A sont comme définis en (a) ci-dessus,
 Z est un carbonyle ou un β -hydroxylethylène et R₃ est un hydrogène, α -méthyle, β -méthyle, =CH₂
 ou α - ou β -OR₂ dans lequel R₂ est identique à R₂ ci-dessus ;

(d) un composé de formule



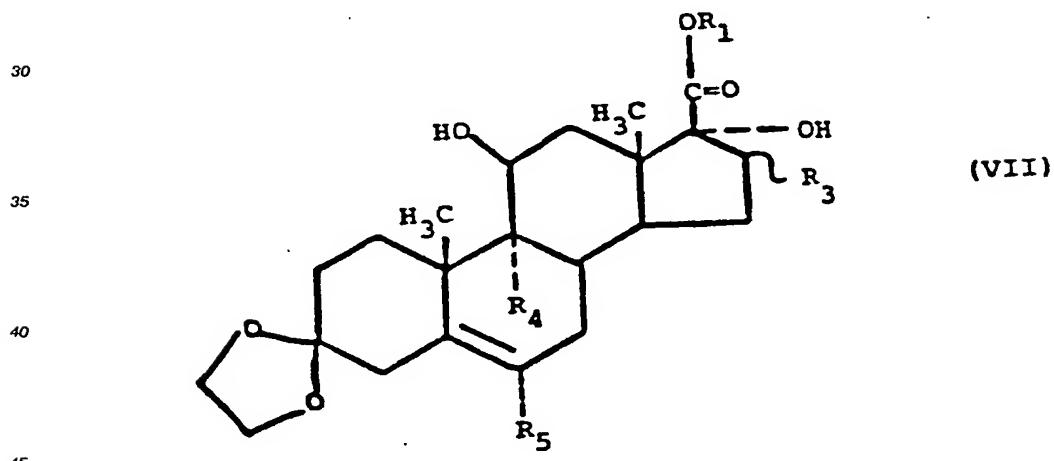
50 dans laquelle R₂, R₄, R₅, et la ligne en pointillé dans le cycle A sont comme définis en (a) ci-dessus,
 Z est un carbonyle ou un β -hydroxyméthylène et R₃ est un hydrogène, un α -méthyle, un β -
 méthyle, =CH₂ ou α - ou β -OR₂ dans lequel R₂ est identique à R₂ ci-dessus ;

(e) un composé de formule



dans laquelle M est un métal alcalin, thallium, métal/2 alcalino-terreux ou NH_4 et R_2 , R_3 , R_4 , R_5 , Z et
 25 la ligne en pointillé dans le cycle A sont comme définis en (a) et (d) ci-dessus :

(f) un composé de formule



où R_3 est un hydrogène, α -méthyle, β -méthyle, ou $\alpha\text{-OR}_2$ ou $\beta\text{-OR}_2$, et R_1 , R_4 et R_5 sont comme
 définis en (a) ci-dessus ;

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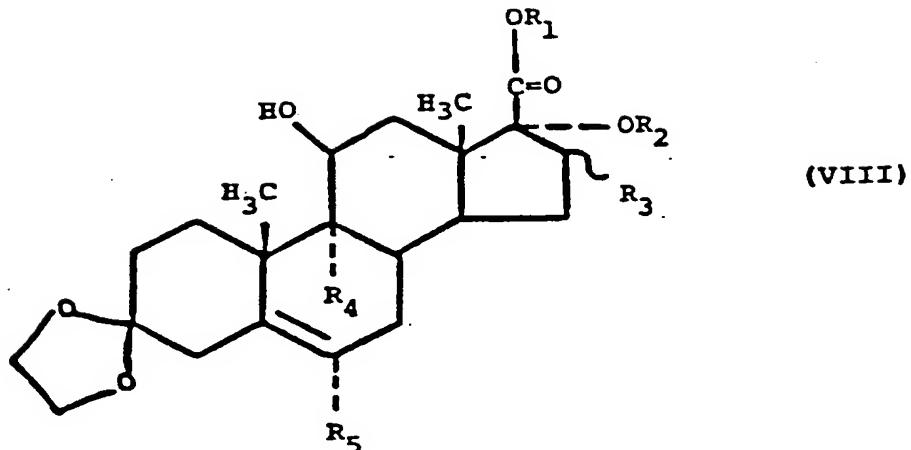
(g) Un composé de formule

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dans laquelle R₃ est un hydrogène, α -méthyle, β -méthyle, α -OR₂ ou β -OR₂, et R₁, R₂, R₄ et R₅ sont comme définis en (a) ci-dessus ;

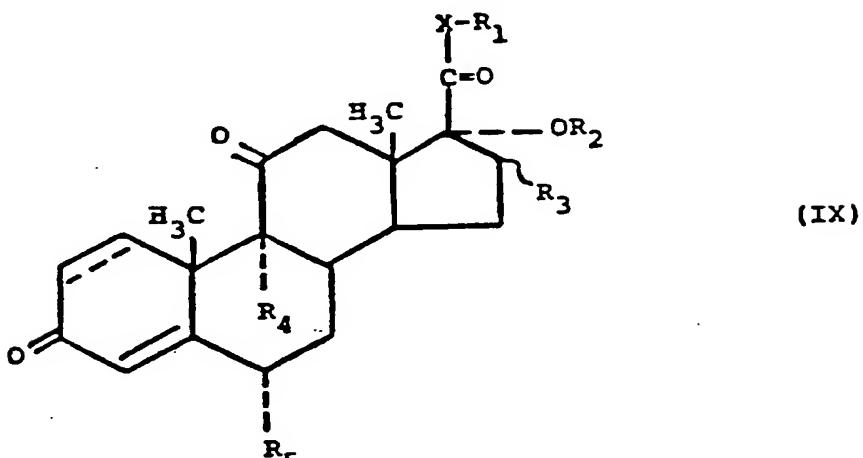
(h) un composé de formule

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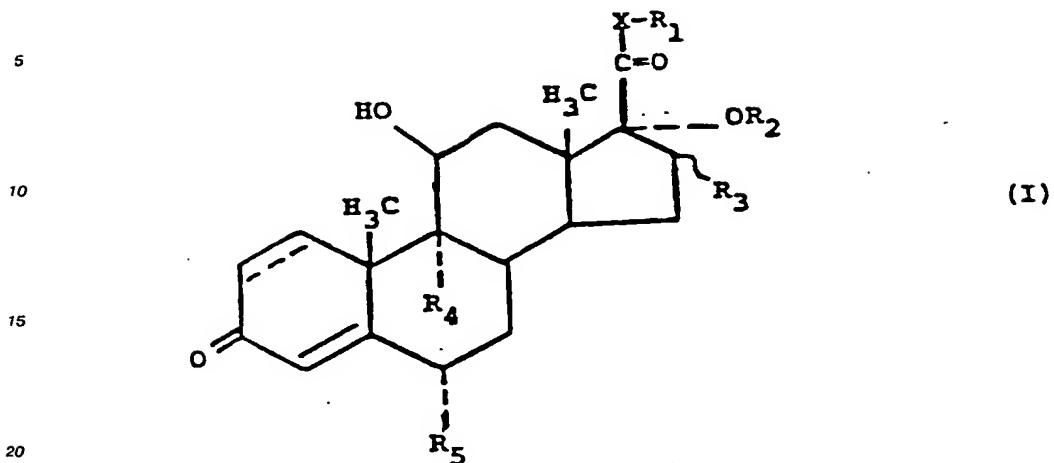


dans laquelle R₁, R₂, R₃, R₄, R₅, X et la ligne en pointillé dans le cycle A sont comme définis en (a) ci-dessus.

50 2. Composé choisi dans le groupe constitué de :

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(a) un composé de formule



dans laquelle :

25 R_1 est un alkyle de C_1-C_6 ; un (monohalo ou polyhalo) alkyle de C_1-C_6 ; $-CH_2COOR_6$ dans lequel R_6 est un alkyle de C_1-C_6 ; $-CH_2-Y$ -alkyle de C_1-C_6 dans lequel Y est $-S-$, $-SO-$, $-SO_2-$ ou $-O-$; ou bien

dans lequel R_6' est un alkyle de C_1-C_6 ou un phényle;

35 R_2 est un alkyle de C_1-C_6 , un cycloalkyle de C_3-C_8 , un phényle, un benzyle ou bien un (monohalo ou polyhalo) alkyle de C_1-C_6 ;

R_3 est un hydrogène, α -hydroxy, α -méthyle, β -méthyle ou bien

dans lequel R_2 est identique à R_2 comme défini ci-avant ;

45 R_4 est un hydrogène ou un fluoro ;

R_5 est un hydrogène ou un fluoro ;

X est $-O-$ ou $-S-$;

et la ligne en pointillé dans le cycle A indique que la liaison 1,2- est saturée ou non saturée;

(b) un sel d'ammonium quaternaire d'un composé de formule (I) dans lequel au moins un des éléments R_1 et R_2 est un groupe alkyle halo-substitué ;

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(c) un composé de la formule

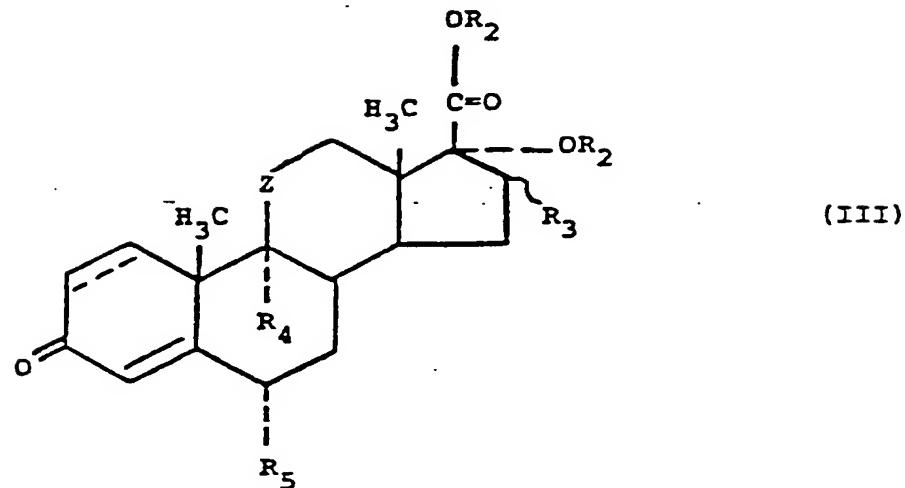
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dans laquelle R_2 , R_4 , R_5 , et la ligne en pointillé dans le cycle A sont comme définis en (a) ci-dessus,
 Z est un carbonyle ou un β -hydroxyméthylène et R_3 est un hydrogène, α -méthyle, β -méthyle,
 $=CH_2$ ou α - ou bien β -OR₂ dans lequel R₂ est identique à R₂ ci-dessus ;

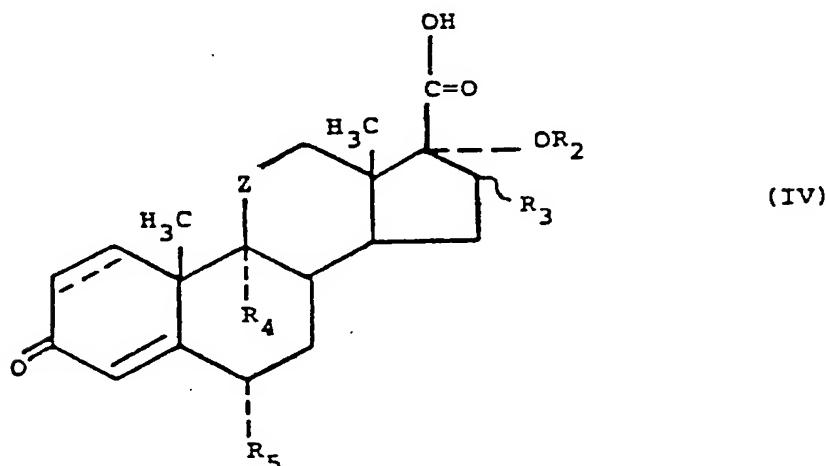
(d) un composé de formule

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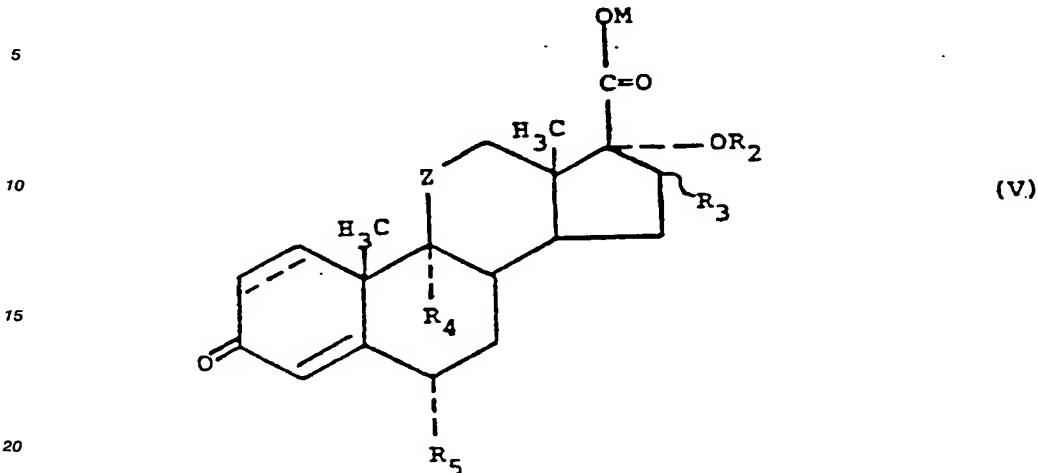
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dans laquelle R₂, R₄, R₅, et la ligne en pointillé dans le cycle A sont comme définis en (a) ci-dessus,
 Z est un carbonyle, ou bien un β -hydroxyméthylène et R₃ est un hydrogène, un α -méthyle, β -
méthyle, $=CH_2$ ou bien α - ou β -OR₂ dans lequel R₂ est identique à R₂ ci-dessus ;

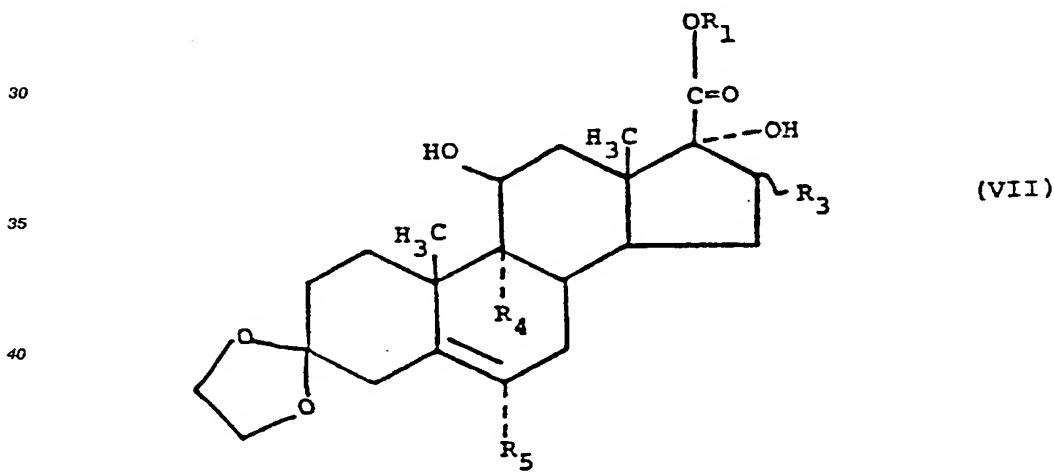
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(e) un composé de formule



25 dans laquelle M est un métal alcalin, thallium, métal/2 alcalino-terreux ou NH_4 et R_2 , R_3 , R_4 , R_5 , Z et la ligne en pointillé dans le cycle A sont comme définis en (a) et (d) ci-dessus ;

(f) composé de formule



50 dans laquelle R_3 est un hydrogène, un α -méthyle, β -méthyle, α - OR_2 ou β - OR_2 , et R_1 , R_4 et R_5 sont comme définis en (a) ci-dessus ;

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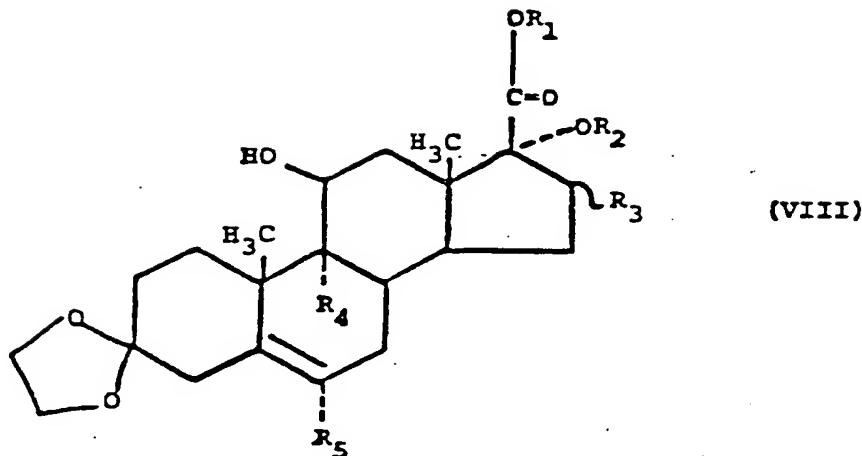
(g) un composé de formule

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dans laquelle R_3 est un hydrogène, un α -méthyle, β -méthyle, α -OR₂ ou β -OR₂, et R₁, R₂, R₄ et R₅ sont comme définis en (a) ci-dessus ;

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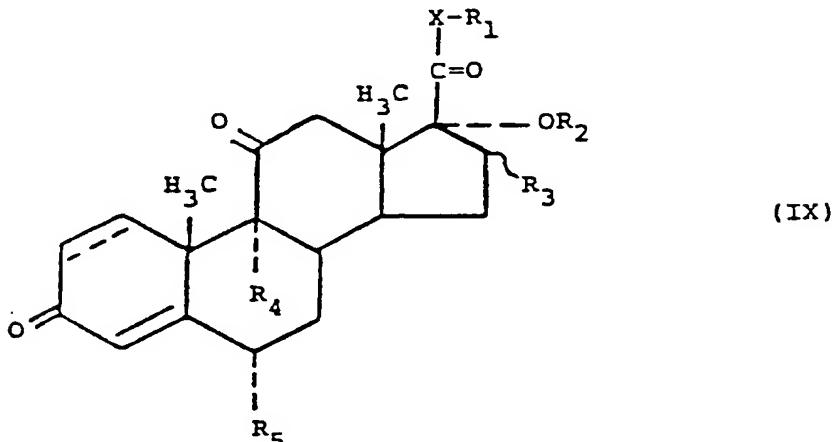
(h) un composé de formule

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dans laquelle R₁, R₂, R₃, R₄, R₅, X et la ligne en pointillé dans le cycle A sont comme définis en (a) ci-dessus.

50 3. Composé selon la revendication 1 ou 2, ledit composé étant un sel d'ammonium quaternaire d'un composé de formule (I) dans lequel au moins un de R₁ et de R₂ est un groupe alkyle halo-substitué.

4. Composé selon la revendication 1, ledit composé ayant la formule de structure (I) dans lequel R₃ est un hydrogène, un α -méthyle, β -méthyle, =CH₂, α -OR₂ ou bien β -OR₂.

55 5. Composé selon la revendication 1 ou 2, ledit composé présentant la formule de structure (I) dans lequel R₁ est un alkyle de C₁-C₆ ou un (monohalo ou polyhalo) alkyle de C₁-C₆.

6. Composé selon la revendication 5 dans lequel le monochloroalkyle de C₁-C₆ est le chlorométhyle.

7. Composé selon l'une au moins des revendications précédentes dans lequel R₂ est un alkyle de C₁-C₆ ou un monohaloalkyle de C₁-C₆.

5 8. Composé selon l'une au moins des revendications précédentes dans lequel R₂ est un cycloalkyle de C₃-C₈, un phényle, un benzyle ou un (monohalo ou polyhalo) alkyle de C₁-C₆.

10 9. Composé selon l'une au moins des revendications précédentes, ledit composé présentant la formule de structure (I) dans lequel X est -O-.

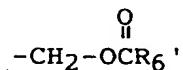
10 10. Composé selon l'une au moins des revendications précédentes dans lequel R₄ et R₅ sont de l'hydrogène.

15 11. Composé selon l'une au moins des revendications précédentes dans lequel au moins un de R₄ et R₅ est un fluoro.

15 12. Composé selon l'une au moins des revendications précédentes dans lequel R₄ est un fluoro et R₅ est un hydrogène.

20 13. Composé selon l'une au moins des revendications précédentes dans lequel R₃ est un α -méthyle ou un β -méthyle.

20 14. Composé selon la revendication 1 ou 2, ledit composé ayant la formule de structure (I) dans lequel R₁ est -CH₂COOR₆, -CH₂-Y-(alkyle de C₁-C₆),



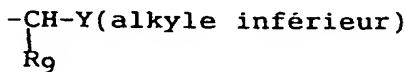
ou -CH₂CONR₇R₈.

35 15. Composé selon la revendication 14 dans lequel au moins un de R₇ et R₈ est un hydrogène ou un alkyle de C₁-C₆.

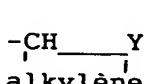
16. Composé selon la revendication 14 dans lequel R₇ et R₈ sont combinés de sorte que -NR₇R₈ représente le résidu d'une amine secondaire monocyclique saturée contenant 5 à 7 atomes de carbone.

40 17. Composé selon la revendication 16 dans lequel -NR₇R₈ représente un morpholino, 1-pyrrolidinyle, 4-benzyle-1-pipérazinyle, perhydro-1,2,4-oxyathiazine-4-yle, 1- ou 4-piperazinyle, 4-méthyl-1-pipérazinyle, piperidino, hexaméthylèneimino, 4-phénylpiperidino, 2-méthyl-1-pyrazolidinyle, 1- ou 2-pyrazolidinyle, 3-méthyl-1-imidazolidinyle, 1- ou 3-imidazolidinyle, 4-benzylpiperidino ou 4-phényl-1-piperazinyle.

45 18. Composé selon la revendication 1, ledit composé ayant la formule de structure (I) dans lequel R₁ est



où R₉ est un hydrogène ou un méthyle, ou bien où R₉ et le groupe alkyle inférieur adjacent à Y sont combinés de sorte que R₁ est



où Y est -S-, -SO-, -SO₂- ou -O- et où le groupe alkylène contient 3 à 10 atomes de carbone, dont au moins 3 et pas plus de 6 sont des atomes d'un cycle.

5 19. Composé selon la revendication 1 ou 2, ledit composé ayant la formule de structure (I) dans laquelle les groupements R₃, R₄ et R₅ et la liaison 1,2-sont identiques à ceux d'un glucocorticostéroïde choisi dans le groupe constitué d'hydrocortisone prednisolone, fludrocortisone, bétaméthasone, dexaméthasone, fluméthasone, fluprednisolone, méthyl prednisolone et paraméthasone.

10 20. Composé selon la revendication 1 ou 2, ledit composé ayant la formule de structure (I) dans laquelle R₃ est α -OR₂, et dans laquelle les groupements R₄ et R₅ et la liaison 1,2- sont identiques à ceux de la triamcinolone.

15 21. Composé selon la revendication 1 ou 2, ledit composé ayant la formule de structure (III),(IV) ou (VIII) dans laquelle Z est un β -hydroxyméthylène et R₂est un alkyle de C₁-C₆ .

20 22. Composé selon la revendication 1 ou 2, ledit composé ayant la formule de structure (VII) dans laquelle Z est un β -hydroxyméthylène et R₁ est un alkyle de C₁-C₆ ou un monohaloalkyle de C₁-C₆ .

23. Composé selon la revendication 1 ou 2, ledit composé ayant la formule de structure (IX) dans laquelle R₁ est un (monohalo ou polyhalo) alkyle de C₁-C₆ .

24. Composé selon la revendication 23 dans lequel R₂ est un alkyle de C₁-C₆ .

25 25. Composé selon la revendication 1 ou 2, ledit composé ayant la formule de structure (IX) dans laquelle R₁ est un alkyle de C₁-C₆ ou un monohaloalkyle de C₁-C₆ ,R₂ est un alkyle de C₁-C₆ ou un monohaloalkyle de C₁-C₆ et X est -O-.

30 26. Composé selon la revendication 25 dans lequel les groupements R₃, R₄ et R₅ et la liaison 1,2-sont identiques à ceux d'un glucocorticostéroïde choisi dans le groupe constitué de cortisone, prednisone, chloroprednisone et méprednisone.

35 27. Composition pharmaceutique d'une matière comprenant une quantité efficace pour une activité anti-inflammatoire d'un composé d'au moins une des revendications précédentes, en combinaison avec un support acceptable pharmaceutiquement non-toxique de façon à convenir à une application topique ou à une autre application locale.

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